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

Summary

EudraCT number	2012-001222-95
Trial protocol	GB NL CZ
Global end of trial date	09 January 2015

Results information

Result version number	v2 (current)
This version publication date	03 December 2019
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Minor corrections

Trial information

Trial identification

Sponsor protocol code	R727-CL-1112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709500
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: ODYSSEY FH II

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.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	10 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2014
Global end of trial reached?	Yes
Global end of trial date	09 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Subjects entered into the 78 weeks double blind treatment period. The main objective of double blind treatment period was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab 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).

All subjects who successfully completed the 78-week double-blind treatment period had the opportunity to participate in an open-label extension study, receiving alirocumab at entry into the open-label extension regardless of the study treatment they had received during the double-blind treatment period.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

All subjects were on a maximally tolerated stable daily dose of statin (atorvastatin, rosuvastatin, or simvastatin) with or without other LMT throughout the duration of the study.

Evidence for comparator: -

Actual start date of recruitment	28 November 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	Norway: 49
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Czech Republic: 75
Country: Number of subjects enrolled	Netherlands: 100
Worldwide total number of subjects	249
EEA total number of subjects	249

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)	198
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 26 sites in 4 countries. Overall, 322 subjects were screened between 28 Nov 2012 and 26 April 2013, 73 of whom were screen failures.

Pre-assignment

Screening details:

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

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Alirocumab 75 mg/up to 150 mg

Arm description:

Alirocumab 75 mg every two weeks (Q2W) added to stable dose of statin with or without LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥70 mg/dL at Week 8.

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

Dosage and administration details:

Alirocumab administered as a subcutaneous (SC) injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

Arm title	Placebo

Arm description:

Placebo matched to alirocumab for 78-week treatment duration.

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:

Placebo matched to alirocumab administered as a SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

Number of subjects in period 1	Alirocumab 75 mg/up to 150 mg	Placebo
Started	167	82
Treated	167	81
Completed	0	0
Not completed	167	82
Related to IMP administration	1	-
Randomized but not treated	-	1
Treatment ongoing	156	78
Adverse event	5	1
Poor compliance to protocol	2	1
Unspecified	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Alirocumab 75 mg/up to 150 mg
Reporting group description:	
Alirocumab 75 mg every two weeks (Q2W) added to stable dose of statin with or without LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥70 mg/dL at Week 8.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to alirocumab for 78-week treatment duration.	

Reporting group values	Alirocumab 75 mg/up to 150 mg	Placebo	Total
Number of subjects	167	82	249
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.2	53.2	
standard deviation	± 12.93	± 12.55	-
Gender categorical Units: Subjects			
Female	81	37	118
Male	86	45	131
Calculated LDL-C in mmol/L			
Calculated LDL-C values were obtained using Friedewald formula.			
Units: mmol/L			
arithmetic mean	3.485	3.471	
standard deviation	± 1.065	± 1.071	-
Calculated LDL-C in mg/dL Units: mg/dL			
arithmetic mean	134.6	134	
standard deviation	± 41.1	± 41.4	-

End points

End points reporting groups

Reporting group title	Alirocumab 75 mg/up to 150 mg
Reporting group description:	
Alirocumab 75 mg every two weeks (Q2W) added to stable dose of statin with or without LMT for 78 weeks. Alirocumab dose up--titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥70 mg/dL at Week 8.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to alirocumab for 78-week treatment duration.	

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

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

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-48.7 (± 1.9)	2.8 (± 2.8)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Alirocumab group was compared to the placebo group using an appropriate contrast statement.	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-51.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.1
upper limit	-44.8

Notes:

[1] - Threshold for significance ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-49.4 (± 1.9)	2.7 (± 2.7)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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 5% level.

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-52.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.7
upper limit	-45.6

Notes:

[2] - Threshold for significance ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-43.8 (± 1.8)	4.6 (± 2.6)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-48.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.7
upper limit	-42.2

Notes:

[3] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 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). mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-44.2 (± 1.8)	4.6 (± 2.6)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg /up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-48.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55
upper limit	-42.5

Notes:

[4] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: percent change				
least squares mean (standard error)	-42.8 (± 1.4)	-3.5 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.1
upper limit	-34.5

Notes:

[5] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). Subjects 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	80		
Units: percent change				
least squares mean (standard error)	-43.2 (± 1.4)	-3.5 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.5
upper limit	-35.1

Notes:

[6] - Threshold for significance ≤ 0.05.

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

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

End point description:

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

off-treatment.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-42.6 (± 1.8)	3.1 (± 2.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-45.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.8
upper limit	-39.7

Notes:

[7] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-43.2 (± 1.7)	3.1 (± 2.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-46.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.3
upper limit	-40.4

Notes:

[8] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Total Cholesterol (Total--C) at Week 24 -- ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-30.6 (± 1.4)	2.1 (± 1.9)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-32.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.4
upper limit	-28.1

Notes:

[9] - Threshold for significance ≤ 0.05.

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

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

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: percent change				
least squares mean (standard error)	-35.4 (± 1.4)	-0.9 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.2
upper limit	-29.8

Notes:

[10] - Threshold for significance ≤ 0.05.

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

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

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-37.9 (± 1.7)	4.1 (± 2.4)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.8
upper limit	-36.2

Notes:

[11] - Threshold for significance ≤ 0.05.

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

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

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-26.6 (± 1.3)	3.4 (± 1.9)		

Statistical analyses

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

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.5
upper limit	-25.4

Notes:

[12] - Threshold for significance ≤ 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	-50.3 (± 2.3)	8.4 (± 3.3)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-58.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-66.8
upper limit	-50.8

Notes:

[13] - Threshold for significance ≤ 0.05.

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

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percentage of subjects				
number (not applicable)	81.4	11.3		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	52.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	20.9
upper limit	130

Notes:

[14] - Threshold for significance ≤ 0.05

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

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

End point description:

Adjusted percentages at Week 24 were 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) (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percentage of subjects				
number (not applicable)	82.1	11.6		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	53.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	21.4
upper limit	132.6

Notes:

[15] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted percentages at Week 24 were obtained from 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 analysis). ITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percentage of subjects				
number (not applicable)	68.2	1.2		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	239.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.6
upper limit	1820.3

Notes:

[16] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted percentages at Week 24 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) (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percentage of subjects				
number (not applicable)	68.8	1.3		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	240.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.4
upper limit	1841.7

Notes:

[17] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted means and standard errors at Week 24 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. Subjects analyzed: subjects of the ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
arithmetic mean (standard error)	-30.3 (± 1.8)	-10 (± 2.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-20.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-14.2

Notes:

[18] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	6 (± 1.2)	-0.8 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [19]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	10.7

Notes:

[19] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted means and standard errors at Week 24 from 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
arithmetic mean (standard error)	-10.4 (± 2)	0.5 (± 2.8)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [20]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	-4.3

Notes:

[20] - Threshold for significance ≤ 0.05.

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 model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. ITT population: all randomized and treated subjects 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: percent change				
least squares mean (standard error)	2.8 (± 0.9)	-1.6 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0062 [21]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	7.5

Notes:

[21] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 12 -- ITT Analysis
End point description:	
Adjusted means and standard errors at Week 12 from 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
arithmetic mean (standard error)	-24.7 (± 1.7)	-5.6 (± 2.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	-13.1

Notes:

[22] - Threshold for significance ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
least squares mean (standard error)	6 (± 1)	-0.8 (± 1.6)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0147 [23]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	7.8

Notes:

[23] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 12 -- ITT Analysis

End point description:

Adjusted means and standard errors at Week 12 from 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	81		
Units: percent change				
arithmetic mean (standard error)	-8.1 (± 2.2)	0.6 (± 3.1)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg 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	Alirocumab 75 mg/up to 150 mg v Placebo

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [24]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.1
upper limit	-1.1

Notes:

[24] - Threshold for significance ≤ 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	Alirocumab 75 mg/up to 150 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	81		
Units: percent change				
least squares mean (standard error)	0.4 (± 0.9)	-1.9 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg v Placebo
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1475 [25]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.5

Notes:

[25] - Threshold for significance ≤ 0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 52

Adverse event reporting additional description:

Treatment emergent adverse events that developed during treatment emergent adverse events period (the time from the first dose of study drug to the last dose of study drug + 70 days (10 weeks) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo matched to alirocumab for 78 week treatment duration.

Reporting group title	Alirocumab 75 mg/up to 150 mg

Reporting group description:

Alirocumab 75 mg Q2W added to stable dose of statin with or without LMT for 78 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥70 mg/dL at Week 8.

Serious adverse events	Placebo	Alirocumab 75 mg/up to 150 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 81 (8.64%)	10 / 167 (5.99%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
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			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (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			
Syncope			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Non-Cardiac chest pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
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 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 81 (1.23%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			

subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis a			
subjects affected / exposed	0 / 81 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 167 (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 mg/up to 150 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 81 (43.21%)	65 / 167 (38.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 81 (8.64%)	14 / 167 (8.38%)	
occurrences (all)	8	16	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	6 / 81 (7.41%)	18 / 167 (10.78%)	
occurrences (all)	14	68	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 81 (1.23%)	9 / 167 (5.39%)	
occurrences (all)	1	12	
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	10 / 167 (5.99%) 15	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 81 (19.75%) 24	18 / 167 (10.78%) 25	
Influenza subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 8	24 / 167 (14.37%) 25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2013	The purpose of this amendment was to: - Change an exclusion criterion from HbA1c >8.5% to HbA1c >9%. - Clarify that repeat testing was allowed for eligibility with respect to Thyroid-stimulating hormone (TSH) laboratory results. - Clarify fulfillment of applicable local regulatory requirements through the Informed consent form (ICF) or a local protocol addendum in women of childbearing potential and add a definition for the duration of required contraception use after discontinuation of the study drug. - Add contingency language to ensure the continuity of study drug treatment without interruption (in the event the manufacturer faced any performance or supply issues of the auto-injector). - Widen some visit windows to allow more scheduling flexibility, and make the visit window for the end of double-blind treatment visit (visit 12, week 78) narrower. - Clarify that reporting of Adverse event of special interests (AESIs) that require accelerated reporting was to be done within 24 hours of the site's learning of the event. - Add neurologic and ophthalmologic events that require additional examinations/procedures and/or referral to a specialist as reportable AESIs that require accelerated reporting. - Define neurologic and ophthalmologic events that did not require additional examinations/procedures and/or referral to a specialist as AESIs that did not require accelerated reporting. - Remove hospitalization for unanticipated coronary revascularization from the list of Clinical events committee (CEC) adjudication categories, and add that all coronary revascularizations was to be submitted to the CEC. - Make miscellaneous administrative corrections and clarifications.
09 April 2014	The purpose of this amendment was to: - Modify the primary efficacy analysis population to the ITT population for the primary and secondary efficacy endpoints, which included assessments both on study treatment and off study treatment through the analysis period. - MMRM was to be used for the primary endpoint and for other continuous secondary endpoints anticipated to have normally distributed data. - For continuous endpoints expected to have non-normally distributed data, the robust regression method was to be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - For binary endpoints, logistic regression method was be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - Primary and key secondary endpoints was to also be analyzed in the mITT population to assess the drug effect during the study treatment period (on-treatment approach). - The list of key and other secondary efficacy endpoints and estimands (ITT estimand or on-treatment estimand) were adjusted. - Update language on CV events to be reported to the CEC for adjudication, and to clarify cerebrovascular events. - Clarify that LDL-C measured and calculated was to be performed at weeks 0 and 24. - Update language on collection of partner pregnancy, per the ODYSSEY program. - Update categorization of AEs (update language on how to record injection site reactions that were not related to study drug). - Make minor corrections/clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported