Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 in Patients With Heterozygous Familial Hypercholesterolemia and LDL-C higher or equal to 160 mg/dL with Their Lipid-Modifying Therapy

Summary

EudraCT number	2012-001096-37
Trial protocol	NL
Global end of trial date	06 January 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	EFC12732

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617655
WHO universal trial number (UTN)	U1111-1128-5459
Other trial identifiers	Study Name: ODYSSEY High FH

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	17 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2014
Global end of trial reached?	Yes
Global end of trial date	06 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab (SAR236553/REGN727) as add-on therapy to stable maximally tolerated daily statin therapy with or without other lipid modifying therapy (LMT) in comparison with placebo after 24 weeks of treatment in subjects with heterozygous familial hypercholesterolemia (heFH) and LDL-C higher than or equal to 160 mg/dL (4.14 mmol/L).

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

Actual start date of recruitment	06 June 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	Netherlands: 11
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	107
EEA total number of subjects	11

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)	93
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 33 centers in 5 countries. A total of 206 subjects were screened between June 2012 and May 2013, 99 of whom were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction (MI) or ischemic stroke, and intensity of statin treatment. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:2 (placebo:alirocumab) ratio after confirmation of selection criteria. 107 subjects were randomized.

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

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

Arm title	Alirocumab 150 mg Q2W

Arm description:

Alirocumab 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.

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

Dosage and administration details:

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

Number of subjects in period 1	Placebo	Alirocumab 150 mg Q2W
Started	35	72
Completed	4	6
Not completed	31	66
Subjects moved	-	2
Other than specified here	4	6
Treatment ongoing	25	51
Adverse event	1	3
Poor compliance to protocol	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo for alirocumab every two weeks (Q2W) on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	

Reporting group values	Placebo	Alirocumab 150 mg Q2W	Total
Number of subjects	35	72	107
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	52.1	49.8	
standard deviation	± 11.2	± 14.2	-
Gender categorical			
Units: Subjects			
Female	13	37	50
Male	22	35	57
Calculated LDL--C in mmol/L			
Calculated LDL-C from Friedewald formula.			
Units: mmol/L			
arithmetic mean	5.205	5.083	
standard deviation	± 1.125	± 1.499	-
Calculated LDL--C in mg/dL			
Units: mg/dL			
arithmetic mean	201	196.3	
standard deviation	± 43.4	± 57.9	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo for alirocumab every two weeks (Q2W) on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT for 78 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to placebo on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 61 weeks)	
Subject analysis set title	Alirocumab 150 mg Q2W
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to Alirocumab 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 58 weeks)	

Primary: Percent Change From Baseline in Calculated LDL-C at Week 24 - ITT Analysis

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

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.6 (± 4.9)	-45.7 (± 3.5)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Alirocumab group was compared to placebo group using an appropriate contrast statement.	

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-39.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.1
upper limit	-27.1

Notes:

[1] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.6 (± 5)	-45.5 (± 3.5)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

Comparison groups	Placebo v Alirocumab 150 mg Q2W

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-38.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51
upper limit	-26.9

Notes:

[2] - Threshold for significance was ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 were obtained 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	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.6 (± 4.6)	-46.9 (± 3.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-40.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.4
upper limit	-29.3

Notes:

[3] - Threshold for significance was ≤ 0.05.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 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	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.6 (± 4.6)	-46.9 (± 3.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-40.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.4
upper limit	-29.2

Notes:

[4] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: percent change				
least squares mean (standard error)	-8.7 (± 3.8)	-39 (± 2.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-30.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.7
upper limit	-20.9

Notes:

[5] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: percent change				
least squares mean (standard error)	-8.7 (± 3.9)	-38.9 (± 2.8)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.7
upper limit	-20.7

Notes:

[6] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.2 (± 4.3)	-41.9 (± 3.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-35.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.3
upper limit	-25.3

Notes:

[7] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.1 (± 4.3)	-41.7 (± 3.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-35.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.2
upper limit	-24.9

Notes:

[8] - Threshold for significance was ≤ 0.05.

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

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-4.8 (± 3.6)	-33.2 (± 2.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-28.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.3
upper limit	-19.6

Notes:

[9] - Threshold for significance was ≤ 0.05.

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

End point title	Percent Change From Baseline in Apo B at Week 12 - ITT Analysis

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: percent change				
least squares mean (standard error)	-9 (± 3.7)	-39.2 (± 2.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.2
upper limit	-21.1

Notes:

[10] - Threshold for significance was ≤ 0.05.

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

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

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-6.9 (± 4.3)	-41.4 (± 3)		

Statistical analyses

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

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.8
upper limit	-24.1

Notes:

[11] - Threshold for significance was ≤ 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	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-5.2 (± 3.5)	-33 (± 2.4)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-27.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.2
upper limit	-19.4

Notes:

[12] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	-3 (± 5.9)	-42.1 (± 4.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-39.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.6
upper limit	-24.6

Notes:

[13] - Threshold for significance was ≤ 0.05.

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

End point title	Percentage of Very High CV Risk Subjects Achieving Calculated LDL-C < 70 mg/dL (<1.81 mmol/L) or High CV Risk Subjects Achieving Calculated LDL-C < 100 mg/dL (<2.59 mmol/L) at Week 24 - 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	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percentage of subjects				
number (not applicable)	5.7	41		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	53.5

Notes:

[14] - Threshold for significance was ≤ 0.05.

Secondary: Percentage of Very High CV Risk Subjects Achieving Calculated LDL-C <

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percentage of subjects				
number (not applicable)	5.7	41.4		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo

Statistical analysis description:

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

Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	54.9

Notes:

[15] - Threshold for significance was ≤ 0.05.

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

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

End point description:

Adjusted means and standard errors at Week 24 from a multiple imputation approach model including

all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population.

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

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
arithmetic mean (standard error)	-8.7 (± 5)	-23.5 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.	
Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0164 [16]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.9
upper limit	-2.7

Notes:

[16] - Threshold for significance was ≤ 0.05.

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

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

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	3.9 (± 2.7)	7.5 (± 1.9)		

Statistical analyses

Statistical analysis title	Alirocumab vs Placebo
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Placebo v Alirocumab 150 mg Q2W
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2745 [17]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	10.2

Notes:

[17] - Threshold for significance was ≤ 0.05.

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

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis
End point description:	
Adjusted means and standard errors at Week 24 from multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 52	

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
arithmetic mean (standard error)	-1.9 (± 4.8)	-10.5 (± 3.3)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: percent change				
least squares mean (standard error)	2 (± 2.1)	5.6 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
arithmetic mean (standard error)	-1.5 (± 5.1)	-23.2 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
least squares mean (standard error)	8 (± 3.4)	7.9 (± 2.4)		

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 multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Fasting triglycerides ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percent change				
arithmetic mean (standard error)	-4.4 (± 5.1)	-9.4 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Apo A-1 at Week 12- - ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo A-1 ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	69		
Units: percent change				
least squares mean (standard error)	1.1 (± 2.2)	4.6 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

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 multiple imputation approach 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:

Up to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percentage of subjects				
number (not applicable)	2.9	32.4		

Statistical analyses

No statistical analyses for this end point

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

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	71		
Units: percentage of subjects				
number (not applicable)	2.9	32.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects exposed to placebo Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 61 weeks).

Reporting group title	Alirocumab 150 Q2W

Reporting group description:

Subjects exposed to Alirocumab 150 mg Q2W on top of stable maximally tolerated daily statin therapy with or without other LMT (mean exposure of 58 weeks).

Serious adverse events	Placebo	Alirocumab 150 Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 35 (11.43%)	8 / 72 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			

subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
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	0 / 35 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 35 (2.86%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid Arthritis			

subjects affected / exposed	1 / 35 (2.86%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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 150 Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 35 (54.29%)	31 / 72 (43.06%)	
Investigations			
Blood Uric Acid Increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 35 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	4	
Injection Site Reaction			
subjects affected / exposed	1 / 35 (2.86%)	6 / 72 (8.33%)	
occurrences (all)	1	7	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	2 / 35 (5.71%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 35 (8.57%)	4 / 72 (5.56%)	
occurrences (all)	5	4	
Dyspepsia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 35 (5.71%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 35 (8.57%)	3 / 72 (4.17%)	
occurrences (all)	4	3	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	8 / 72 (11.11%)	
occurrences (all)	1	8	
Nasopharyngitis			
subjects affected / exposed	4 / 35 (11.43%)	8 / 72 (11.11%)	
occurrences (all)	4	10	
Sinusitis			
subjects affected / exposed	2 / 35 (5.71%)	4 / 72 (5.56%)	
occurrences (all)	2	4	
Urinary Tract Infection			
subjects affected / exposed	0 / 35 (0.00%)	5 / 72 (6.94%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2013	- Changes in the reporting of AEs: 1. Addition of neurological and ophthalmologic events in the list of Adverse Events of Special Interest (AESIs). 2. Addition of pregnancy of male subject's partner as an AESI with immediate notification to comply with an update in the company procedure. 3. Safety reporting timelines changed from "within 1 working day" to "within 24 hours" for serious adverse events and AESI with immediate notification. - Change in the screening period duration and the window for the training visit: 1. Added the information on a possible contingency strategy in the event the manufacturer faced any performance or supply issues of the auto-injector in order to ensure the continuity of the study treatment without interruption. - Clarification for some safety laboratory parameters: 1. Red blood cell distribution width (RDW) and reticulocyte count were added as hematology laboratory parameters. 2. Reticulocyte count was no longer assessed reflexively but assessed systematically on all study samples. - Clarification was provided regarding the type of cardiovascular (CV) events to be submitted to the Clinical Events Committee (CEC) for adjudication. - Added a clarification on how to handle subjects randomized and not treated with the IMP. - Added information on the collection of family medical history. - Clarified the wording related to the possibility for a heFH subject having completed the double-blind treatment period to enter an open-label extension (OLE). Other minor changes including administrative changes, clarification, inconsistency corrections, or omissions/typo errors are not listed.
26 February 2014	- Modified the primary efficacy analysis population and the statistical analysis methodology: 1. Modified the primary efficacy analysis population to the intent-to-treat (ITT) population for the primary and secondary efficacy endpoints, which included assessments both on study treatment and off study treatment through the analysis period. 2. Primary and key secondary endpoints were also to be analyzed in the modified ITT (mITT) population to assess the drug effect during the study treatment period (on-treatment approach). 3. The list of key and other secondary efficacy endpoints and estimand (ITT estimand or on-treatment estimand) used were adjusted. - Updated language on CV events to be reported to the CEC for adjudication and included a clarification on CV events. - Updated language on collection of partner pregnancy as per other protocol in the ODYSSEY Phase 3 program. - Categorization of AEs (updated language on how to record injection site reactions that were not related to study drug).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: