Clinical trial results:
A Randomized, Double-Blind, Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 over 24 weeks in Patients with Hypercholesterolemia

Summary

EudraCT number	2011-001424-38
Trial protocol	BE FI NL
Global end of trial date	09 July 2013

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	A poster - EFC11716

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01644474
WHO universal trial number (UTN)	U1111-1124-1167
Other trial identifiers	STUDY NAME: ODYSSEY MONO

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2013
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) every 2 weeks (Q2W) as monotherapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in subjects with hypercholesterolemia at moderate cardiovascular (CV) risk.

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:

Concomitant medications were to be kept to a minimum during the study. However, if they were considered necessary for the subject's welfare, and were unlikely to interfere with the investigational medicinal product (IMPs), they could be given at a stable dose (when possible), at the discretion of the Investigator.

Evidence for comparator: -

Actual start date of recruitment	02 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	103
EEA total number of subjects	54

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)	84
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 centers in 4 countries. A total of 204 subjects were screened between July 2012 and November 2012, 101 of whom were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Randomization was stratified according to the diabetes mellitus status. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:1 (alirocumab:ezetimibe) ratio after confirmation of selection criteria. 103 subjects were randomized.

Period 1

Period 1 title	Overall Study (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 autoinjectors and packaged identically. Ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labeled with a double-blind label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ezetimibe 10 mg

Arm description:

Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Ezetrol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One over-encapsulated tablet once daily.

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.

Arm title	Alirocumab 75/Up to 150 mg Q2W

Arm description:

Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Arm type	Experimental

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

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh, or outer area of the upper arm by self--injection.

Investigational medicinal product name	Placebo (for Ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule once daily.

Number of subjects in period 1	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W
Started	51	52
Completed	44	44
Not completed	7	8
Consent withdrawn by subject	-	1
'Other than specified '	2	1
Adverse Event	4	5
Poor compliance to protocol	1	-
Patient moved	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ezetimibe 10 mg
Reporting group description:	
Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.	
Reporting group title	Alirocumab 75/Up to 150 mg Q2W
Reporting group description:	
Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.	

Reporting group values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W	Total
Number of subjects	51	52	103
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.6	60.8	
standard deviation	± 5.3	± 4.6	-
Gender categorical			
Units: Subjects			
Female	24	24	48
Male	27	28	55
Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	138.3	141.1	
standard deviation	± 24.5	± 27.1	-
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	3.58	3.65	
standard deviation	± 0.6	± 0.7	-

End points

End points reporting groups

Reporting group title	Ezetimibe 10 mg
Reporting group description:	
Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.	
Reporting group title	Alirocumab 75/Up to 150 mg Q2W
Reporting group description:	
Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.	
Subject analysis set title	Ezetimibe 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to Ezetimibe 10 mg (mean exposure of 22 weeks).	
Subject analysis set title	Alirocumab 75/Up to 150 mg Q2W
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W (mean exposure of 22 weeks).	

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

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

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-15.6 (± 3.1)	-47.2 (± 3)		

Statistical analyses

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

Comparison groups	Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-31.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.2
upper limit	-23

Notes:

[1] - Threshold for significance was ≤ 0.05.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-19.6 (± 2.6)	-48.1 (± 2.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

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	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-28.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.7
upper limit	-21.2

Notes:

[2] - Threshold for significance ≤ 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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percent change				
least squares mean (standard error)	-11 (± 2.4)	-36.7 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-25.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-19.2

Notes:

[3] - 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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-15.1 (± 2.9)	-40.6 (± 2.8)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-25.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.5
upper limit	-17.4

Notes:

[4] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Total Cholestrol (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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-10.9 (± 2.2)	-29.6 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg

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	-18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.7
upper limit	-12.7

Notes:

[5] - 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 24 regardless of status on- or off-treatment. Apo B ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percent change				
least squares mean (standard error)	-11.7 (± 2.1)	-37.3 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-25.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	-19.8

Notes:

[6] - 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 24 regardless of status on- or off-treatment. non-HDL-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-16.7 (± 2.4)	-42.5 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-25.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.4
upper limit	-19.2

Notes:

[7] - Threshold for significance ≤ 0.05.

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

End point title	Percent Change From Baseline in Total Cholestrol (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 24 regardless of status on- or off-treatment. Total-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	-12 (± 1.7)	-30.3 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.1
upper limit	-13.5

Notes:

[8] - Threshold for significance ≤ 0.05.

Secondary: Percentage of Subjects Achieving Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

End point title	Percentage of 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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of subjects				
number (not applicable)	32.2	88.1		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

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	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	34.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.7
upper limit	139

Notes:

[9] - Threshold for significance ≤ 0.05.

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

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

End point description:

Adjusted percentages from multiple imputation approach including all available post-baseline data from Week 4 to Week 24 regardless of status on-- or off--treatment. ITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of subjects				
number (not applicable)	2.4	59.4		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	69.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	556

Notes:

[10] - 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 24 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 24	

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
arithmetic mean (standard error)	-12.3 (± 3.8)	-16.7 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Ezetimibe

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	Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4013 [11]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	5.9

Notes:

[11] - 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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	1.6 (± 1.9)	6 (± 1.9)		

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 24 regardless of status on- or off-treatment. HDL-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
least squares mean (standard error)	1.6 (± 2)	9 (± 2)		

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

End point type	Secondary

End point timeframe:

From Baseline Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
arithmetic mean (standard error)	-14.2 (± 3.7)	-17.2 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
arithmetic mean (standard error)	-10.8 (± 4.3)	-11.9 (± 4.2)		

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 24 regardless of status on- or off-treatment. Fasting

triglycerides ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percent change				
arithmetic mean (standard error)	-2.3 (± 3.5)	-12.2 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Apoprotein 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 24 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 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percent change				
least squares mean (standard error)	-0.6 (± 1.6)	4.7 (± 1.6)		

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 24 regardless of status on- or off-treatment. Apo A-1 ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percent change				
arithmetic mean (standard error)	-2.2 (± 1.4)	2.3 (± 1.4)		

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 the final visit (Week 32) 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 administration (capsule or injection, whichever came first) up the day of the last double-blind IMP injection + 70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Ezetimibe 10 mg

Reporting group description:

Subjects exposed to Ezetimibe 10 mg (mean exposure of 22 weeks).

Reporting group title	Alirocumab 75/Up to 150 mg Q2W

Reporting group description:

Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W (mean exposure of 22 weeks).

Serious adverse events	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
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			
Bone Erosion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (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	Ezetimibe 10 mg	Alirocumab 75/Up to 150 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 51 (52.94%)	25 / 52 (48.08%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Headache			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	
occurrences (all)	2	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 51 (3.92%)	6 / 52 (11.54%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	3 / 51 (5.88%)	3 / 52 (5.77%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Back Pain			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 51 (5.88%)	6 / 52 (11.54%)	
occurrences (all)	3	6	
Nasopharyngitis			
subjects affected / exposed	8 / 51 (15.69%)	12 / 52 (23.08%)	
occurrences (all)	9	16	
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 51 (9.80%)	2 / 52 (3.85%)	
occurrences (all)	6	2	
Urinary Tract Infection			

subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 52 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2013	1. Change in reporting of adverse events - safety reporting timelines was changed from "within 1 working day" to "within 24 hours" for serious adverse events and adverse events of special interest (AESI) with immediate notification. - Addition of pregnancy of male subject's partner as an AESI with immediate notification. 2. Clarification for some safety laboratory parameters - Red blood cell distribution width and reticulocyte count added as hematology laboratory parameters. - Reticulocyte count no longer assessed reflexively but rather systematically on all study samples. 3. Precision added in the definition of the investigational medicinal product – ezetimibe capsule. 4. Highlighted the need for an effective method of contraception in women of childbearing potential throughout the study treatment.

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.

Due to administrative error in the automated process (which was detected after database lock), planned dose up-titration criteria for LDL-C levels was changed from ≥100 mg/dL to ≥70 mg/dL.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25606700