EU Clinical Trials Register

Clinical trial results:
A Randomized, Double-Blind Study of the Efficacy and Safety of REGN727 Added on to Rosuvastatin versus Ezetimibe Added-on to Rosuvastatin versus Rosuvastatin Dose Increase in Patients Who are Not Controlled on Rosuvastatin

Summary

EudraCT number	2012-002333-11
Trial protocol	DE ES GB IT
Global end of trial date	08 May 2014

Results information

Result version number	v2 (current)
This version publication date	08 April 2020
First version publication date	06 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	R727-CL-1118

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01730053
WHO universal trial number (UTN)	-
Other trial identifiers	Study ID: ODYSSEY OPTIONS 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	Final
Date of interim/final analysis	08 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab as add-on therapy to rosuvastatin in comparison with ezetimibe as add-on therapy to rosuvastatin, and in comparison with doubling the rosuvastatin dose, after 24 weeks of treatment in subjects with hypercholesterolemia at high cardiovascular (CV) risk.

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:

Lipid-modifying therapies (LMT) that were allowed as background therapy included fish oils with ≥1000 mg of omega-3 fatty acids, fenofibrate, bile acid-binding sequestrates (eg, cholestyramine), and niacin. Doses of these medications were to remain stable for at least 4 weeks (at least 6 weeks for fenofibrate) before the screening visit, during the screening period, and during the double-blind treatment period.

Evidence for comparator: -

Actual start date of recruitment	23 October 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	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	United States: 183
Country: Number of subjects enrolled	Australia: 21
Worldwide total number of subjects	305
EEA total number of subjects	71

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)	188
From 65 to 84 years	115
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 79 sites in 8 countries. Overall, 672 subjects were screened between 29 October 2012 and 27 September 2013, 367 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 or ischemic stroke, and intensity of statin treatment (rosuvastatin 10 or 20 mg). Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:1:1:1:1:1 ratio after confirmation of selection criteria.

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	Investigator, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Rosuvastatin 20 mg

Arm description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received rosuvastatin 20 mg once daily (QD), placebo for alirocumab every two weeks (Q2W), and placebo for ezetimibe QD added to stable Lipid-Modifying Therapy (LMT) for 24 weeks.

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

Dosage and administration details:

Rosuvastatin over-encapsulated tablets.

Investigational medicinal product name	Placebo (for Alirocumab and Ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for injection
Routes of administration	Oral use, 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. Placebo matched to ezetimibe over-encapsulated tablet.

Arm title	Ezetimibe 10 mg + Rosuvastatin 10 mg

Arm description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 10 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Arm type	Active comparator

Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	Crestor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin over-encapsulated tablets.

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

Dosage and administration details:

Ezetimibe over-encapsulated tablet.

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:

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

Arm title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Arm description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 10 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	Crestor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin over-encapsulated tablets.

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 SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

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:

Placebo matched to ezetimibe over-encapsulated tablet.

Arm title	Rosuvastatin 40 mg

Arm description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received rosuvastatin 40 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.

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

Dosage and administration details:

Rosuvastatin over-encapsulated tablets.

Investigational medicinal product name	Placebo (for Alirocumab and Ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for injection
Routes of administration	Oral use, 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. Placebo matched to ezetimibe over-encapsulated tablet.

Arm title	Ezetimibe 10 mg + Rosuvastatin 20 mg

Arm description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 20 mg QD, and placebo for alirocumab Q2W added to stable LMT 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:

Ezetimibe over-encapsulated tablet.

Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	Crestor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 20 mg over-encapsulated tablets.

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:

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

Arm title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg

Arm description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

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 SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin over-encapsulated tablets.

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:

Placebo matched to ezetimibe over-encapsulated tablet.

Number of subjects in period 1	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Started	48	48	49
Treated	48	48	49
Completed	43	34	38
Not completed	5	14	11
Physician decision	-	-	-
Adverse event	2	6	3
Other than specified	2	6	5
Subject moved	-	-	1
Poor compliance to protocol	1	2	2

Number of subjects in period 1	Rosuvastatin 40 mg	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg
Started	53	53	54
Treated	53	53	54
Completed	45	44	41
Not completed	8	9	13
Physician decision	1	-	-
Adverse event	3	2	2
Other than specified	4	7	9
Subject moved	-	-	-

Poor compliance to protocol	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	Rosuvastatin 20 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 10 mg at baseline, received rosuvastatin 20 mg once daily (QD), placebo for alirocumab every two weeks (Q2W), and placebo for ezetimibe QD added to stable Lipid-Modifying Therapy (LMT) for 24 weeks.

Reporting group title	Ezetimibe 10 mg + Rosuvastatin 10 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 10 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 10 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Reporting group title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 10 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 10 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

Reporting group title	Rosuvastatin 40 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 20 mg at baseline, received rosuvastatin 40 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.

Reporting group title	Ezetimibe 10 mg + Rosuvastatin 20 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 20 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 20 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Reporting group title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg
Reporting group description:	

Subjects, who were receiving rosuvastatin 20 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

Reporting group values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects	48	48	49
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.5	60.4	62.2
standard deviation	± 11.15	± 10.38	± 11.11
Gender categorical			
Units: Subjects			
Female	15	22	18
Male	33	26	31
Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	105.9	102.4	107.3

standard deviation	± 36	± 41.9	± 26.4
LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.743	2.653	2.78
standard deviation	± 0.933	± 1.085	± 0.684

Reporting group values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg
Number of subjects	53	53	54
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.6	63.1	57.9
standard deviation	± 10.11	± 10.2	± 8.86
Gender categorical			
Units: Subjects			
Female	15	22	26
Male	38	31	28
Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	112.9	119	118.3
standard deviation	± 43.3	± 48	± 32.2
LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.924	3.082	3.065
standard deviation	± 1.122	± 1.243	± 0.834

Reporting group values	Total		
Number of subjects	305		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	118		
Male	187		
Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
LDL-C in mmol/L			
Units: mmol/L			

arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Rosuvastatin 20 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 10 mg at baseline, received rosuvastatin 20 mg once daily (QD), placebo for alirocumab every two weeks (Q2W), and placebo for ezetimibe QD added to stable Lipid-Modifying Therapy (LMT) for 24 weeks.	
Reporting group title	Ezetimibe 10 mg + Rosuvastatin 10 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 10 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 10 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.	
Reporting group title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 10 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 10 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.	
Reporting group title	Rosuvastatin 40 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 20 mg at baseline, received rosuvastatin 40 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.	
Reporting group title	Ezetimibe 10 mg + Rosuvastatin 20 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 20 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 20 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.	
Reporting group title	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg
Reporting group description:	
Subjects, who were receiving rosuvastatin 20 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.	

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 Friedewald 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-16.3 (± 4.1)	-14.4 (± 4.4)	-50.6 (± 4.2)	-15.9 (± 7.1)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-11 (± 7.2)	-36.3 (± 7.1)		

Statistical analyses

Statistical analysis title	Alirocumab v Rosuvastatin 20 mg

Statistical analysis description:

Alirocumab group was compared to the corresponding active control group using an appropriate contrast statement.

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-34.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-49.2
upper limit	-19.3

Notes:

[1] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab v Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

As described in statistical analysis 1 of the endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-36.1
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-51.5
upper limit	-20.7

Notes:

[2] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab v Rosuvastatin 40 mg
Statistical analysis description:	
As described in statistical analysis 1 of the endpoint.	
Comparison groups	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg v Rosuvastatin 40 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0453 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.3
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-45.8
upper limit	5.1

Notes:

[3] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab v Ezetimibe 10 mg + Rosuvastatin 20 mg
Statistical analysis description:	
As described in statistical analysis 1 of the endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.3

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-50.9
upper limit	0.3

Notes:

[4] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained using the Friedewald formula. 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 24 (i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first) (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 24

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	46	48	50
Units: percent change				
least squares mean (standard error)	-18.3 (± 3.3)	-20.3 (± 3.6)	-53.5 (± 3.5)	-17 (± 6.9)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent change				
least squares mean (standard error)	-16.5 (± 6.9)	-41.5 (± 6.9)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

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 1.25 % level.

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-47.4
upper limit	-23

Notes:

[5] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 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	-33.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-45.9
upper limit	-20.5

Notes:

[6] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Rosuvastatin 40 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Rosuvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0131 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-49.2
upper limit	0.2

Notes:

[7] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained using the Friedewald formula. 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 (ITT analysis). ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-17.1 (± 4.1)	-17.4 (± 4.2)	-49.6 (± 4.1)	-22.1 (± 5.3)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-19.3 (± 5.4)	-32.3 (± 5.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-47.4
upper limit	-17.9

Notes:

[8] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-47
upper limit	-17.5

Notes:

[9] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained using the Friedewald formula. 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 24 (i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first) (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	46	48	50
Units: percent change				
least squares mean (standard error)	-17.2 (± 3.6)	-20.3 (± 3.8)	-52.6 (± 3.6)	-22.9 (± 5.2)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percent change				
least squares mean (standard error)	-21.8 (± 5.2)	-35.1 (± 5.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.3

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-48.2
upper limit	-22.5

Notes:

[10] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.3
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-45.6
upper limit	-19

Notes:

[11] - Threshold for significance ≤ 0.0125.

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 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	51
Units: percent change				
least squares mean (standard error)	-7.3 (± 3)	-9.7 (± 3.1)	-36.5 (± 3.1)	-9.8 (± 4.1)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: percent change				
least squares mean (standard error)	-11.2 (± 4.3)	-28.3 (± 4.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg v Rosuvastatin 20 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-40.1
upper limit	-18.3

Notes:

[12] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg v Ezetimibe 10 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.8

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-37.9
upper limit	-15.7

Notes:

[13] - Threshold for significance ≤ 0.0125.

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 24 (i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first). 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 24

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	42	43	50
Units: percent change				
least squares mean (standard error)	-8.8 (± 2.6)	-11.2 (± 2.7)	-39.5 (± 2.6)	-12.7 (± 4)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percent change				
least squares mean (standard error)	-12.6 (± 4.1)	-30.4 (± 4.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

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

for rosuvastatin 10 mg baseline stratification).

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.7
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-40.1
upper limit	-21.3

Notes:

[14] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28.3
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-38
upper limit	-18.7

Notes:

[15] - Threshold for significance ≤ 0.0125.

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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-11.3 (± 3.4)	-13.4 (± 3.7)	-42.7 (± 3.5)	-11.2 (± 5.1)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-12.9 (± 5.2)	-31.4 (± 5.2)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.4
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-43.9
upper limit	-18.9

Notes:

[16] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.3
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-42.1
upper limit	-16.4

Notes:

[17] - Threshold for significance ≤ 0.0125.

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 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first). 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 24

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	46	48	50
Units: percent change				
least squares mean (standard error)	-12.9 (± 2.8)	-17.5 (± 3.1)	-45.7 (± 2.9)	-14.9 (± 4.2)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		

Units: percent change				
least squares mean (standard error)	-18.2 (± 4.2)	-35.6 (± 4.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.8
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-43.2
upper limit	-22.4

Notes:

[18] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-39.1
upper limit	-17.3

Notes:

[19] - Threshold for significance ≤ 0.0125.

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 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-8.3 (± 2.4)	-8.7 (± 2.6)	-28.9 (± 2.5)	-8.5 (± 3.6)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-12.4 (± 3.6)	-20.6 (± 3.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.6

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-29.4
upper limit	-11.8

Notes:

[20] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.3

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-29.3
upper limit	-11.2

Notes:

[21] - Threshold for significance ≤ 0.0125.

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 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	51
Units: percent change				
least squares mean (standard error)	-8.1 (± 3.2)	-12.1 (± 3.3)	-36.1 (± 3.2)	-13.7 (± 3.3)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: percent change				
least squares mean (standard error)	-14.3 (± 3.3)	-29 (± 3.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28.1
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-39.7
upper limit	-16.5

Notes:

[22] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-35.7
upper limit	-12.3

Notes:

[23] - Threshold for significance ≤ 0.0125.

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 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-11.7 (± 3.5)	-16.3 (± 3.6)	-41.2 (± 3.5)	-18 (± 3.6)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-18.7 (± 3.7)	-29.8 (± 3.6)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.5
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-42.1
upper limit	-16.9

Notes:

[24] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [25]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24.9
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-37.7
upper limit	-12.2

Notes:

[25] - Threshold for significance ≤ 0.0125.

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

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-8.9 (± 2.6)	-11.8 (± 2.7)	-29 (± 2.6)	-13.8 (± 2.8)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-13.9 (± 2.8)	-19.4 (± 2.7)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification).

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-20.1
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-29.4
upper limit	-10.7

Notes:

[26] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-17.2
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-26.7
upper limit	-7.7

Notes:

[27] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained from Friedewald formula. 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percentage of subjects				
number (not applicable)	45	57.2	84.9	40.1

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percentage of subjects				
number (not applicable)	52.2	66.7		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg v Rosuvastatin 20 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.4
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	2.6
upper limit	59.5

Notes:

[28] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [29]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.4
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	1.8
upper limit	40.5

Notes:

[29] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained from Friedewald formula. 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 24 i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	46	48	50
Units: percentage of subjects				
number (not applicable)	47	60.5	86.4	41.3

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percentage of subjects				
number (not applicable)	54.8	70.4		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	2.58
upper limit	88.2

Notes:

[30] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [31]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.9
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	1.7
upper limit	56.7

Notes:

[31] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained from Friedewald formula. 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percentage of subjects				
number (not applicable)	31.3	43.1	77.8	29.9

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percentage of subjects				
number (not applicable)	43.6	60.1		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	18.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	3.6
upper limit	96.2

Notes:

[32] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	2.5
upper limit	53.1

Notes:

[33] - Threshold for significance ≤ 0.0125.

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:

Calculated LDL-C values were obtained from Friedewald formula. 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 24 i.e. up to 21 days after last injection or 3 days after the last capsule [rosuvastatin or ezetimibe], whichever came first (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	46	48	50
Units: percentage of subjects				
number (not applicable)	34.8	46.7	76.5	30.6

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percentage of subjects				
number (not applicable)	45.1	66.1		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.	
Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	20.3
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	2.4
upper limit	67.7

Notes:

[34] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.7
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	2.4
upper limit	67.7

Notes:

[35] - Threshold for significance ≤ 0.0125.

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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
arithmetic mean (standard error)	-4 (± 4.3)	-4.3 (± 4.5)	-27.9 (± 4.1)	-5.2 (± 4.8)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
arithmetic mean (standard error)	-5.8 (± 4.6)	-22.7 (± 5.1)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Rosuvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-23.9

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-38.6
upper limit	-9.1

Notes:

[36] - Threshold for significance ≤ 0.0125.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Rosuvastatin 10 mg

Statistical analysis description:

Analysis description as per the statistical analysis 1 of this endpoint.

Comparison groups	Ezetimibe 10 mg + Rosuvastatin 10 mg v Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [37]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-23.6
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-39
upper limit	-8.2

Notes:

[37] - Threshold for significance ≤ 0.0125.

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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	1.7 (± 2.4)	4 (± 2.5)	9.1 (± 2.4)	1.5 (± 2.3)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-1.8 (± 2.3)	7.2 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab vs Rosuvastatin 20 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant for rosuvastatin 10 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a robust regression model.	
Comparison groups	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg v Rosuvastatin 20 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0311 [38]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	7.4
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-1.2
upper limit	16.1

Notes:

[38] - Threshold for significance ≤ 0.0125.

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 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	-1.8 (± 4.5)	-8.3 (± 4.8)	-11.2 (± 4.6)	-9.9 (± 4.1)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-11.1 (± 4.3)	-8.7 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM 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	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	51
Units: percent change				

least squares mean (standard error)	5.4 (± 1.9)	5 (± 1.9)	6.7 (± 1.9)	2.9 (± 1.9)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: percent change				
least squares mean (standard error)	-0.9 (± 1.9)	6.7 (± 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 a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Lipoprotein (a) ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
arithmetic mean (standard error)	-0.7 (± 3.5)	-3.9 (± 3.6)	-20.7 (± 3.5)	3.5 (± 4.2)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				

arithmetic mean (standard error)	7.9 (± 4.1)	-16 (± 4.2)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM 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 12

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	0.7 (± 2.1)	0.2 (± 2.2)	5.9 (± 2.1)	0.6 (± 2.5)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	3.1 (± 2.5)	8 (± 2.5)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis
End point description:	
Adjusted means and standard errors at Week 12 from a multiple imputation approach 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 12	

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	48	52
Units: percent change				
least squares mean (standard error)	8.1 (± 4.1)	-8.2 (± 4.2)	-14 (± 4.1)	-2.7 (± 4)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	53		
Units: percent change				
least squares mean (standard error)	-12.4 (± 4)	-10.1 (± 4)		

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 12	

End point values	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 10 mg	Rosuvastatin 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	44	44	51
Units: percent change				
least squares mean (standard error)	4 (± 1.6)	2.6 (± 1.6)	4.3 (± 1.6)	0.9 (± 1.8)

End point values	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Rosuvastatin 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: percent change				
least squares mean (standard error)	1.8 (± 1.8)	9.1 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to Week 24

Adverse event reporting additional description:

Treatment emergent adverse events that developed during treatment emergent adverse events period (the time period from the first double-blind injection of study drug up to the day of last injection + 70 days) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Rosuvastatin 20 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received rosuvastatin 20 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.

Reporting group title	Ezetimibe 10 mg + Rosuvastatin 10 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 10 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Reporting group title	Alirocumab 75/up to 150 + Rosuvastatin 20 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 20 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

Reporting group title	Rosuvastatin 40 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received rosuvastatin 40 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.

Reporting group title	Ezetimibe 10 mg + Rosuvastatin 20 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 20 mg at baseline, received ezetimibe 10 mg QD, rosuvastatin 20 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Reporting group title	Alirocumab 75/up to 150 + Rosuvastatin 10 mg

Reporting group description:

Subjects, who were receiving rosuvastatin 10 mg at baseline, received alirocumab 75 mg Q2W, rosuvastatin 10 mg QD, and placebo for ezetimibe QD added to stable LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) at Week 8, based on baseline disease characteristic and medical history.

Serious adverse events	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75/up to 150 + Rosuvastatin 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)	5 / 48 (10.42%)	4 / 54 (7.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Small cell lung cancer metastatic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Iron deficiency anaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-Cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Spinal cord infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rosuvastatin 40 mg	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75/up to 150 + Rosuvastatin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	2 / 49 (4.08%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Small cell lung cancer metastatic			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Subarachnoid haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-Cardiac chest pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Spinal cord infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Alirocumab 75/up to 150 + Rosuvastatin 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 48 (22.92%)	11 / 48 (22.92%)	15 / 54 (27.78%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	2 / 54 (3.70%)
occurrences (all)	4	1	2
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	2 / 48 (4.17%)	0 / 48 (0.00%)	3 / 54 (5.56%)
occurrences (all)	3	0	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	2 / 48 (4.17%)	2 / 54 (3.70%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	0 / 54 (0.00%)
occurrences (all)	1	3	0
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 48 (2.08%)	3 / 48 (6.25%)	4 / 54 (7.41%)
occurrences (all)	2	3	5
Pain in extremity			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 48 (4.17%)	2 / 54 (3.70%)
occurrences (all)	1	2	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	4 / 54 (7.41%)
occurrences (all)	3	0	4

Non-serious adverse events	Rosuvastatin 40 mg	Ezetimibe 10 mg + Rosuvastatin 20 mg	Alirocumab 75/up to 150 + Rosuvastatin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 53 (37.74%)	12 / 53 (22.64%)	11 / 49 (22.45%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 53 (5.66%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences (all)	4	0	0
Dizziness			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 53 (5.66%)	0 / 53 (0.00%)	0 / 49 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	3 / 49 (6.12%)
occurrences (all)	1	1	3
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	4 / 49 (8.16%)
occurrences (all)	2	1	4
Myalgia			

subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	5 / 53 (9.43%)	2 / 53 (3.77%)	2 / 49 (4.08%)
occurrences (all)	5	2	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 53 (11.32%)	3 / 53 (5.66%)	2 / 49 (4.08%)
occurrences (all)	6	3	2
Upper respiratory tract infection			
subjects affected / exposed	6 / 53 (11.32%)	4 / 53 (7.55%)	2 / 49 (4.08%)
occurrences (all)	7	4	2

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: - Redefine the exclusion of subjects with HbA 1c >8.5% to HbA 1c >9%. - Clarify that a repeat lab was allowed for Thyroid-stimulating hormone (TSH) eligibility laboratory results. - Clarify fulfillment of applicable local regulatory requirements through the informed consent form 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. - Clarify LMTs that were allowed as background therapy. - 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). - Remove hospitalization for unanticipated coronary revascularization from the list of Clinical Events Committee (CEC) adjudication categories, and add that all coronary revascularizations would be submitted to the CEC. - Clarify that reporting of Adverse event of special interest (AESI) that required accelerated reporting would be done within 24 hours of learning of the event. - Make miscellaneous administrative clarifications.
08 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 would include assessments both on study treatment and off study treatment through the analysis period. - An MMRM would 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 would be used to test the treatment group differences and missing data would be handled using multiple imputation approach. - For binary endpoints, logistic regression method would be used to test the treatment group differences and missing data would be handled using multiple imputation approach. - Supportive analyses had been added for the primary and secondary efficacy endpoints, pooling treatment arms across the dose regimens. - Primary and key secondary endpoints would 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. - For safety, the initial review of data would be based on the pooled dose regimens, with the individual treatment groups within the rosuvastatin dose regimens as supportive. - Update language on cardiovascular events to be reported to the CEC for adjudication, and to clarify cerebrovascular events. - Clarify that LDL-C measured and calculated would be performed at weeks 0 and 24. - Update language on collection of partner pregnancy data, 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