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

Summary

EudraCT number	2012-002344-24
Trial protocol	DE ES IT GB
Global end of trial date	06 May 2014

Results information

Result version number	v1
This version publication date	18 December 2019
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	R727-CL-1110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01730040
WHO universal trial number (UTN)	-
Other trial identifiers	Study ID: ODYSSEY OPTIONS I

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	10 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 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 atorvastatin in comparison with ezetimibe as add-on therapy to atorvastatin, in comparison with doubling the atorvastatin dose, or in comparison with a therapy switch from atorvastatin to rosuvastatin, 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	24 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	Australia: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	United States: 255
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	355
EEA total number of subjects	59

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)	192
From 65 to 84 years	162
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 85 sites in 9 countries. Overall, 859 subjects were screened between 24 October 2012 and 26 September 2013, 504 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 (atorvastatin 20 or 40 mg). Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:1:1:1:1:1:1 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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Atorvastatin 40 mg

Arm description:

Subjects, who were receiving atorvastatin 20 mg at baseline, received atorvastatin 40 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	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 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 + Atorvastatin 20 mg

Arm description:

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

Arm type	Active comparator

Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin over-encapsulated tablets.

Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia®
Pharmaceutical forms	Tablet
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 + Atorvastatin 20 mg

Arm description:

Subjects, who were receiving atorvastatin 20 mg at baseline, received Alirocumab 75 mg Q2W, atorvastatin 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	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 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.

Arm title	Atorvastatin 80 mg

Arm description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received Atorvastatin 80 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	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 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	Rosuvastatin 40 mg

Arm description:

Subjects, who were receiving atorvastatin 40 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 + Atorvastatin 40 mg

Arm description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 40 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	Zetia®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ezetimibe over-encapsulated tablet.

Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 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 + Atorvastatin 40 mg

Arm description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received alirocumab 75 mg Q2W, atorvastatin 40 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	Atorvastatin
Investigational medicinal product code	
Other name	Lipitor®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Started	57	55	57
Treated	57	55	57
Completed	44	40	46
Not completed	13	15	11
Physician decision	-	-	-
Randomized but not treated	-	-	-
Adverse event	4	3	5
Other than specified	7	8	5
Subject moved	-	-	1
Poor compliance to protocol	2	4	-

Number of subjects in period 1	Atorvastatin 80 mg	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg
Started	47	45	47
Treated	47	45	46
Completed	39	39	40
Not completed	8	6	7
Physician decision	-	-	1
Randomized but not treated	-	-	1
Adverse event	3	1	1
Other than specified	5	5	4
Subject moved	-	-	-
Poor compliance to protocol	-	-	-

Number of subjects in period 1	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Started	47
Treated	47
Completed	38
Not completed	9
Physician decision	1
Randomized but not treated	-
Adverse event	2
Other than specified	4
Subject moved	1
Poor compliance to protocol	1

Baseline characteristics

Reporting groups	
Reporting group title	Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received atorvastatin 40 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 + Atorvastatin 20 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 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 + Atorvastatin 20 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received Alirocumab 75 mg Q2W, atorvastatin 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	Atorvastatin 80 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received Atorvastatin 80 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.	
Reporting group title	Rosuvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 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 + Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 40 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.	
Reporting group title	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received alirocumab 75 mg Q2W, atorvastatin 40 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects	57	55	57
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63	65.7	62.2
standard deviation	± 9.91	± 8.96	± 10.03
Gender categorical Units: Subjects			
Female	22	24	24
Male	35	31	33

Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	100.3	100.4	103.9
standard deviation	± 29.8	± 29.5	± 34.9
LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.957	2.599	2.692
standard deviation	± 0.773	± 0.765	± 0.905

Reporting group values	Atorvastatin 80 mg	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg
Number of subjects	47	45	47
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.2	57.5	63.9
standard deviation	± 10.89	± 9.96	± 10.33
Gender categorical			
Units: Subjects			
Female	14	13	11
Male	33	32	36
Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	108.6	109.8	98.9
standard deviation	± 37.5	± 39	± 29.2
LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.813	2.844	2.562
standard deviation	± 0.97	± 1.011	± 0.756

Reporting group values	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	Total	
Number of subjects	47	355	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.2		
standard deviation	± 10.36	-	
Gender categorical			
Units: Subjects			
Female	16	124	
Male	31	231	

Low density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C from Friedewald formula.			
Units: mg/dL			
arithmetic mean	116.4		
standard deviation	± 37.4	-	
LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	3.016		
standard deviation	± 0.968	-	

End points

End points reporting groups

Reporting group title	Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received atorvastatin 40 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 + Atorvastatin 20 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 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 + Atorvastatin 20 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 20 mg at baseline, received Alirocumab 75 mg Q2W, atorvastatin 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	Atorvastatin 80 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received Atorvastatin 80 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.	
Reporting group title	Rosuvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 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 + Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 40 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.	
Reporting group title	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Reporting group description:	
Subjects, who were receiving atorvastatin 40 mg at baseline, received alirocumab 75 mg Q2W, atorvastatin 40 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 from 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-5 (± 4.6)	-20.5 (± 4.7)	-44.1 (± 4.5)	-4.8 (± 4.2)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-21.4 (± 4.2)	-22.6 (± 4.3)	-54 (± 4.3)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-55.9
upper limit	-22.2

Notes:

[1] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg

Statistical analysis description:

As described in statistical analysis 1 of the endpoint.

Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-40.7
upper limit	-6.5

Notes:

[2] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg v Atorvastatin 80 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-49.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-65
upper limit	-33.5

Notes:

[3] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.6

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-48.4
upper limit	-16.9

Notes:

[4] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-47.4
upper limit	-15.4

Notes:

[5] - Threshold for significance ≤ 0.01.

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 from 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 [whatever atorvastatin, 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	47
Units: percent change				

least squares mean (standard error)	-6.1 (± 4.6)	-23.7 (± 4.7)	-48.6 (± 4.5)	-5 (± 4.4)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-22.9 (± 4.4)	-24.5 (± 4.5)	-57.8 (± 4.5)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 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 hierarchical order. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 1% level.

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-42.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-59.2
upper limit	-25.7

Notes:

[6] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24.9

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-41.9
upper limit	-7.8

Notes:

[7] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-52.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-69.2
upper limit	-36.5

Notes:

[8] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-51.3
upper limit	-18.6

Notes:

[9] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-33.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-50
upper limit	-16.8

Notes:

[10] - Threshold for significance ≤ 0.01.

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 from 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 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-8.5 (± 3.9)	-22.6 (± 3.9)	-48.4 (± 3.8)	-14.5 (± 3.2)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				

least squares mean (standard error)	-23.3 (± 3.2)	-29.7 (± 3.2)	-50.5 (± 3.2)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-54
upper limit	-25.6

Notes:

[11] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-40
upper limit	-11.6

Notes:

[12] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-36
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-47.7
upper limit	-24.3

Notes:

[13] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-39.2
upper limit	-15.4

Notes:

[14] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.9

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-32.8
upper limit	-8.9

Notes:

[15] - Threshold for significance ≤ 0.01.

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 from 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 [whatever atorvastatin, rosuvastatin or ezetimibe], whichever came first) (on-treatment analysis). mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	47
Units: percent change				
least squares mean (standard error)	-9.2 (± 3.1)	-27.1 (± 3.1)	-53.7 (± 3.1)	-14.6 (± 3.2)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-23.3 (± 3.2)	-30.7 (± 3.2)	-50.9 (± 3.2)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-55.8
upper limit	-33.1

Notes:

[16] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-38
upper limit	-15.2

Notes:

[17] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-36.3

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-48.1
upper limit	-24.5

Notes:

[18] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.7
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-39.6
upper limit	-15.8

Notes:

[19] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-32.2
upper limit	-8.2

Notes:

[20] - Threshold for significance ≤ 0.01.

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	53	45
Units: percent change				
least squares mean (standard error)	-4.4 (± 3.5)	-10.1 (± 3.6)	-33.7 (± 3.4)	-3.5 (± 3.3)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	45	42	
Units: percent change				
least squares mean (standard error)	-10.9 (± 3.2)	-14.3 (± 3.3)	-41.9 (± 3.4)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.3

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-42
upper limit	-16.6

Notes:

[21] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-36.6
upper limit	-10.7

Notes:

[22] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-38.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-50.8
upper limit	-26

Notes:

[23] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-43.2
upper limit	-18.6

Notes:

[24] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-40.1
upper limit	-15.1

Notes:

[25] - Threshold for significance ≤ 0.01.

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 (ie. up to 21 days after last injection or 3 days after the last capsule [whatever atorvastatin, 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	50	44
Units: percent change				
least squares mean (standard error)	-5.1 (± 3.3)	-12.6 (± 3.5)	-37.7 (± 3.2)	-4.4 (± 3.4)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	44	41	
Units: percent change				
least squares mean (standard error)	-12.8 (± 3.4)	-16.3 (± 3.4)	-42.7 (± 3.5)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-44.6
upper limit	-20.6

Notes:

[26] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	

Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-37.3
upper limit	-12.8

Notes:

[27] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-38.3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-51.2
upper limit	-25.4

Notes:

[28] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.8

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-42.6
upper limit	-17.1

Notes:

[29] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-39.4
upper limit	-13.4

Notes:

[30] - Threshold for significance ≤ 0.01.

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-6.3 (± 3.9)	-15.1 (± 4)	-36.7 (± 3.9)	-6.5 (± 3.6)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-17.4 (± 3.6)	-21 (± 3.7)	-47.6 (± 3.7)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-44.7
upper limit	-16.1

Notes:

[31] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [32]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-21.6

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-36.1
upper limit	-7.1

Notes:

[32] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-41.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-54.7
upper limit	-27.5

Notes:

[33] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-43.7
upper limit	-16.6

Notes:

[34] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-40.3
upper limit	-12.8

Notes:

[35] - Threshold for significance ≤ 0.01.

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 [whatever atorvastatin, 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	47
Units: percent change				
least squares mean (standard error)	-7.5 (± 3.8)	-18.1 (± 4)	-40.5 (± 3.7)	-7 (± 3.7)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	

Units: percent change				
least squares mean (standard error)	-18.4 (± 3.7)	-23.3 (± 3.8)	-50.5 (± 3.8)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-33
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-47
upper limit	-19

Notes:

[36] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [37]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-36.6
upper limit	-8.1

Notes:

[37] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-43.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-57.4
upper limit	-29.7

Notes:

[38] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-46
upper limit	-18.3

Notes:

[39] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [40]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.3

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-41.4
upper limit	-13.2

Notes:

[40] - Threshold for significance ≤ 0.01.

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-4 (± 2.7)	-11.2 (± 2.8)	-27.1 (± 2.7)	-4.8 (± 2.8)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-11.7 (± 2.8)	-15.2 (± 2.9)	-33.6 (± 2.9)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

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

	Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [41]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-32.9
upper limit	-13.2

Notes:

[41] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [42]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-15.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-25.8
upper limit	-5.8

Notes:

[42] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [43]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28.9

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-39.4
upper limit	-18.4

Notes:

[43] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-21.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-32.4
upper limit	-11.4

Notes:

[44] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [45]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-18.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-29.1
upper limit	-7.7

Notes:

[45] - Threshold for significance ≤ 0.01.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	53	45
Units: percent change				
least squares mean (standard error)	-6.9 (± 2.8)	-13.1 (± 2.8)	-38.4 (± 2.7)	-9.5 (± 2.5)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	45	42	
Units: percent change				
least squares mean (standard error)	-14.1 (± 2.5)	-20.3 (± 2.5)	-36.2 (± 2.5)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-41.6
upper limit	-21.3

Notes:
[46] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [47]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-35.4
upper limit	-15.2

Notes:
[47] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [48]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.7
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-35.9
upper limit	-17.5

Notes:
[48] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-31.5
upper limit	-12.9
Variability estimate	Standard deviation

Notes:

[49] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [50]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-15.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-25.2
upper limit	-6.6

Notes:

[50] - Threshold for significance ≤ 0.01.

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-7.1 (± 3.2)	-17.2 (± 3.2)	-40.6 (± 3.2)	-13 (± 2.6)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-19.8 (± 2.7)	-27.5 (± 2.7)	-42.3 (± 2.7)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant)	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [51]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-33.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-45.3
upper limit	-21.6

Notes:

[51] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [52]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-23.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-35.2
upper limit	-11.6

Notes:

[52] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [53]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-39
upper limit	-19.6

Notes:

[53] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [54]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.5

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-32.3
upper limit	-12.7

Notes:

[54] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [55]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-14.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-24.7
upper limit	-4.9

Notes:

[55] - Threshold for significance ≤ 0.01.

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 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-6.5 (± 2.4)	-13.2 (± 2.4)	-29 (± 2.4)	-9.9 (± 2.1)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	-13.5 (± 2.1)	-19.2 (± 2.1)	-29 (± 2.1)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [56]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-22.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-31.4
upper limit	-13.8

Notes:

[56] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [57]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-15.8

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-24.6
upper limit	-7

Notes:

[57] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [58]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-19.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-26.9
upper limit	-11.4

Notes:

[58] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [59]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-15.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-23.3
upper limit	-7.6

Notes:

[59] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [60]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-9.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-17.7
upper limit	-1.9

Notes:

[60] - Threshold for significance ≤ 0.01.

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

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

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percentage of subjects				
number (not applicable)	34.5	68.4	87.2	18.5

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percentage of subjects				
number (not applicable)	62.2	65.1	84.6	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [61]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.7
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	3.9
upper limit	71.7

Notes:

[61] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 20 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 20 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0284 [62]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.8
upper limit	14.6

Notes:

[62] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [63]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	83.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	11.6
upper limit	596.8

Notes:

[63] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025 [64]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1.3
upper limit	38.3

Notes:

[64] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg
Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [65]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.1

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1.6
upper limit	52.2

Notes:

[65] - Threshold for significance ≤ 0.01.

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

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

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule [whatever atorvastatin, 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	47
Units: percentage of subjects				
number (not applicable)	37.8	72.2	91.2	18.5

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percentage of subjects				
number (not applicable)	64	66.2	90	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant) for atorvastatin 40 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [66]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	128.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	14.2
upper limit	1157

Notes:

[66] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [67]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1.6
upper limit	75.4

Notes:

[67] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:

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

Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [68]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.7
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1.8
upper limit	101.1

Notes:

[68] - Threshold for significance ≤ 0.01.

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

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

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to week 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percentage of subjects				
number (not applicable)	16	50.3	79.2	10.2

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percentage of subjects				
number (not applicable)	42.2	54.2	77.2	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant) for atorvastatin 40 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [69]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	116.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	14.7
upper limit	927.5

Notes:

[69] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [70]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	2.5
upper limit	68.8

Notes:

[70] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [71]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1.9
upper limit	51.9

Notes:

[71] - Threshold for significance ≤ 0.01.

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

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

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule [whatever atorvastatin, 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	47
Units: percentage of subjects				
number (not applicable)	20	55.1	82.3	10.5

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percentage of subjects				

number (not applicable)	42.4	55.3	83.7	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant) for atorvastatin 40 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [72]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	162.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	17.3
upper limit	1520.5

Notes:

[72] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [73]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	19.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	3.1
upper limit	126.3

Notes:

[73] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [74]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	2.2
upper limit	88.1

Notes:

[74] - Threshold for significance ≤ 0.01.

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
arithmetic mean (standard error)	-20.2 (± 4)	-10.6 (± 4.4)	-23.6 (± 4)	-9.7 (± 4.1)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				

arithmetic mean (standard error)	-4.9 (± 3.7)	0.2 (± 3.9)	-30.8 (± 4.1)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant) for atorvastatin 40 mg baseline stratification). Statistical analysis used a multiple imputation approach followed by a robust regression model.	
Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [75]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-21.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-36.3
upper limit	-5.9

Notes:

[75] - Threshold for significance ≤ 0.01.

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 + Atorvastatin 40 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [76]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-25.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-40.2
upper limit	-11.6

Notes:

[76] - Threshold for significance ≤ 0.01.

Statistical analysis title	Alirocumab vs Ezetimibe 10 mg + Atorvastatin 40 mg

Statistical analysis description:	
Analysis description as per the statistical analysis 1 of this endpoint.	
Comparison groups	Ezetimibe 10 mg + Atorvastatin 40 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [77]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-31
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-45.6
upper limit	-16.4

Notes:

[77] - Threshold for significance ≤ 0.01.

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	1.9 (± 2)	-0.1 (± 2.1)	4.8 (± 2)	4.7 (± 2.7)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				

least squares mean (standard error)	5.7 (± 2.7)	2 (± 2.7)	7.7 (± 2.7)	

Statistical analyses

Statistical analysis title	Alirocumab vs Atorvastatin 80 mg

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant) for atorvastatin 40 mg baseline stratification).

Comparison groups	Atorvastatin 80 mg v Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4456 [78]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.9
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-7
upper limit	12.9

Notes:

[78] - Threshold for significance ≤ 0.01.

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. ITT population: all randomized and treated subjects with one baseline and at least one post-baseline fasting triglycerides value on- or off-treatment.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
arithmetic mean (standard error)	-6.7 (± 3.7)	-3.3 (± 4.1)	-12 (± 3.7)	-7.3 (± 4.1)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
arithmetic mean (standard error)	-0.5 (± 4)	-13.9 (± 4.1)	-19.1 (± 4.1)	

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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	53	45
Units: percent change				
least squares mean (standard error)	1.2 (± 1.5)	1 (± 1.6)	7.6 (± 1.5)	2.2 (± 2)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	45	42	
Units: percent change				
least squares mean (standard error)	4.7 (± 1.9)	-1.8 (± 1.9)	5.8 (± 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 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
arithmetic mean (standard error)	-11.7 (± 4)	-5.4 (± 4)	-24 (± 4)	-1.6 (± 4.5)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
arithmetic mean (standard error)	11.5 (± 4.6)	7.9 (± 4.5)	-27.9 (± 4.5)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
least squares mean (standard error)	-3.2 (± 1.8)	-1.7 (± 1.8)	4.1 (± 1.8)	3 (± 2.6)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
least squares mean (standard error)	4.6 (± 2.7)	4.6 (± 2.7)	8.5 (± 2.7)	

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 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	55	47
Units: percent change				
arithmetic mean (standard error)	-4.7 (± 4.2)	0.5 (± 4.2)	-12.4 (± 4.2)	-4.6 (± 4)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	46	46	
Units: percent change				
arithmetic mean (standard error)	-3.7 (± 4.1)	-16.8 (± 4)	-12.1 (± 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 24

End point values	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 20 mg	Atorvastatin 80 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	53	45
Units: percent change				
least squares mean (standard error)	-0.8 (± 1.5)	1.7 (± 1.4)	5.4 (± 1.4)	1.6 (± 1.7)

End point values	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Alirocumab 75 mg/up to 150 mg + Atorvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	45	42	
Units: percent change				
least squares mean (standard error)	5.6 (± 1.7)	1.6 (± 1.7)	9.4 (± 1.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 24

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Atorvastatin 40 mg

Reporting group description:

Subjects, who were receiving atorvastatin 20 mg at baseline, received atorvastatin 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 + Atorvastatin 20 mg

Reporting group description:

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

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

Reporting group description:

Subjects, who were receiving atorvastatin 20 mg at baseline, received Alirocumab 75 mg Q2W, atorvastatin 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	Atorvastatin 80 mg

Reporting group description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received Atorvastatin 80 mg QD, placebo for alirocumab Q2W, and placebo for ezetimibe QD added to stable LMT for 24 weeks.

Reporting group title	Rosuvastatin 40 mg

Reporting group description:

Subjects, who were receiving atorvastatin 40 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 + Atorvastatin 40 mg

Reporting group description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received ezetimibe 10 mg QD, atorvastatin 40 mg QD, and placebo for alirocumab Q2W added to stable LMT for 24 weeks.

Reporting group title	Alirocumab 75/ up to 150 + Atorvastatin 40 mg

Reporting group description:

Subjects, who were receiving atorvastatin 40 mg at baseline, received alirocumab 75 mg Q2W, atorvastatin 40 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	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75/up to 150 + Atorvastatin 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)	5 / 55 (9.09%)	3 / 57 (5.26%)

number of deaths (all causes) number of deaths resulting from adverse events	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Seroma			
subjects affected / exposed	1 / 57 (1.75%)	0 / 55 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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 / 57 (0.00%)	0 / 55 (0.00%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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 arrest			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Non-Cardiac chest pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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			
Anxiety			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Intervertebral disc protrusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	1 / 57 (1.75%)
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			
Diverticulitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 55 (0.00%)	0 / 57 (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
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (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
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (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

Serious adverse events	Atorvastatin 80 mg	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 47 (8.51%)	2 / 45 (4.44%)	2 / 46 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	0 / 46 (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			
Seroma			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Vascular disorders			

Aortic aneurysm			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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 complete			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	0 / 46 (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 arrest			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Coronary artery disease			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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			
Chest pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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-Cardiac chest pain			

subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	0 / 46 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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			
Diverticulitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (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
Pneumonia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	0 / 46 (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	Alirocumab 75/ up to 150 + Atorvastatin 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Atrioventricular block complete				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac chest pain				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	0 / 47 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				

subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Alirocumab 75/up to 150 + Atorvastatin 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 57 (29.82%)	24 / 55 (43.64%)	15 / 57 (26.32%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasopharyngitis			
subjects affected / exposed	1 / 57 (1.75%)	3 / 55 (5.45%)	1 / 57 (1.75%)
occurrences (all)	1	3	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 57 (3.51%)	2 / 55 (3.64%)	0 / 57 (0.00%)
occurrences (all)	3	2	0
Contusion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences (all)	0	5	0
Ligament sprain			
subjects affected / exposed	3 / 57 (5.26%)	3 / 55 (5.45%)	0 / 57 (0.00%)
occurrences (all)	3	3	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	2 / 57 (3.51%)
occurrences (all)	0	1	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)	2 / 55 (3.64%)	0 / 57 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	0 / 55 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 57 (7.02%)	1 / 55 (1.82%)	1 / 57 (1.75%)
occurrences (all)	4	1	1
Nausea			

subjects affected / exposed	3 / 57 (5.26%)	3 / 55 (5.45%)	1 / 57 (1.75%)
occurrences (all)	3	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 55 (5.45%)	2 / 57 (3.51%)
occurrences (all)	1	4	3
Back pain			
subjects affected / exposed	2 / 57 (3.51%)	3 / 55 (5.45%)	3 / 57 (5.26%)
occurrences (all)	2	3	3
Muscle spasms			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	4 / 57 (7.02%)
occurrences (all)	0	1	6
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 57 (1.75%)	1 / 55 (1.82%)	1 / 57 (1.75%)
occurrences (all)	1	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 57 (3.51%)	4 / 55 (7.27%)	2 / 57 (3.51%)
occurrences (all)	3	4	2
Urinary tract infection			
subjects affected / exposed	3 / 57 (5.26%)	5 / 55 (9.09%)	1 / 57 (1.75%)
occurrences (all)	3	6	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 55 (1.82%)	0 / 57 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Atorvastatin 80 mg	Rosuvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 47 (38.30%)	23 / 45 (51.11%)	12 / 46 (26.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasopharyngitis			
subjects affected / exposed	3 / 47 (6.38%)	4 / 45 (8.89%)	0 / 46 (0.00%)
occurrences (all)	3	4	0
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	2 / 47 (4.26%)	3 / 45 (6.67%)	0 / 46 (0.00%)
occurrences (all)	2	4	0
Contusion			
subjects affected / exposed	0 / 47 (0.00%)	3 / 45 (6.67%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Ligament sprain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 45 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	5 / 46 (10.87%)
occurrences (all)	1	0	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 47 (2.13%)	3 / 45 (6.67%)	1 / 46 (2.17%)
occurrences (all)	1	6	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 47 (6.38%)	2 / 45 (4.44%)	0 / 46 (0.00%)
occurrences (all)	3	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)	3 / 45 (6.67%)	2 / 46 (4.35%)
occurrences (all)	1	6	3
Nausea			
subjects affected / exposed	5 / 47 (10.64%)	3 / 45 (6.67%)	1 / 46 (2.17%)
occurrences (all)	5	4	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 45 (2.22%)	1 / 46 (2.17%)
occurrences (all)	1	2	1
Back pain			
subjects affected / exposed	2 / 47 (4.26%)	2 / 45 (4.44%)	0 / 46 (0.00%)
occurrences (all)	2	3	0
Muscle spasms			

subjects affected / exposed	1 / 47 (2.13%)	1 / 45 (2.22%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 47 (0.00%)	3 / 45 (6.67%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 47 (4.26%)	3 / 45 (6.67%)	5 / 46 (10.87%)
occurrences (all)	2	3	6
Urinary tract infection			
subjects affected / exposed	4 / 47 (8.51%)	1 / 45 (2.22%)	3 / 46 (6.52%)
occurrences (all)	4	2	3
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	3 / 46 (6.52%)
occurrences (all)	0	1	3

Non-serious adverse events	Alirocumab 75/ up to 150 + Atorvastatin 40 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 47 (40.43%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasopharyngitis			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1 0 / 47 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1 4 / 47 (8.51%) 4 0 / 47 (0.00%) 0		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection	2 / 47 (4.26%) 2 3 / 47 (6.38%) 3		

subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	 0 / 47 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	The purpose of this amendment was to: - Add an open-label 4-week atorvastatin baseline dose (20 mg or 40 mg) regimen run-in period during the screening period for subjects who, at the discretion of the Investigator, have not been on a stable dose of atorvastatin (20 mg or 40 mg) for 4 weeks, are being switched from another statin to atorvastatin, or are not on a statin but should be according to local guidance. - 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 (ICF) or a local protocol addendum in women of childbearing potential and add a definition for the duration of required contraception use after discontinuation of the study drug. - 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 events (AEs) of interest that required accelerated reporting would be done within 24 hours of learning of the event. - Make miscellaneous administrative clarifications.
09 April 2014	The purpose of this amendment was to: - Modify the primary efficacy analysis population to the ITT population for the primary and secondary efficacy endpoints, which would include assessments both on study treatment and off study treatment through the analysis period. - An Mixed effect model with repeated measures (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 groups across the baseline 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 baseline dose regimens, with the individual treatment groups within the atorvastatin baseline dose regimens as supportive.- Update language on CV events to be reported to the CEC for adjudication, and to clarify cerebrovascular events.- Clarify that LDL-C measured and calculated 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