Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab in Patients with Primary Hypercholesterolemia

Summary

EudraCT number	2013-002343-29
Trial protocol	GB HU SK BG NO
Global end of trial date	28 April 2015

Results information

Result version number	v3 (current)
This version publication date	02 December 2019
First version publication date	22 May 2016
Version creation reason	• Correction of full data set Minor corrections

Trial information

Trial identification

Sponsor protocol code	R727-CL-1308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01926782
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: ODYSSEY CHOICE 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	26 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy, long-term safety, and tolerability of alirocumab 300 mg every 4 weeks (Q4W), in comparison with placebo, as well as its potential as a starting regimen.

The dose regimen of 75 mg every 2 weeks (Q2W), as used in other studies, was added as a calibrator.

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:

The study was conducted in 2 separate populations concurrently: subjects receiving concomitant statin therapy and subjects not receiving concomitant statin therapy.

Subjects receiving concomitant statin were to receive stable daily doses of rosuvastatin, atorvastatin, or simvastatin for at least 4 weeks.

Background treatment with other lipid-modifying therapy (LMT) was allowed for all patients, provided they had been on a stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to study entry.

Evidence for comparator: -

Actual start date of recruitment	25 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 17
Country: Number of subjects enrolled	Slovakia: 50
Country: Number of subjects enrolled	United Kingdom: 63
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	United States: 576
Worldwide total number of subjects	803
EEA total number of subjects	186

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)	518
From 65 to 84 years	282
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 97 sites in 8 countries. A total of 1491 subjects were screened between September 2013 and April 2014, 688 of whom were screen failures. Screen failures were mainly due to inclusion criteria not met.

Pre-assignment

Screening details:

Randomization was stratified according to statin therapy (with/ without) and cardiovascular risk (moderate vs. high/very high) within the population receiving concomitant statin. Assignment to treatment arms was done using an Interactive Voice/Web Response System in 2:1:4 (Placebo: 75 mg: 300 mg) 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	Placebo Q2W with Concomitant Statin

Arm description:

Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) with stable statin therapy for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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 Q2W/Up 150 mg Q2W with Concomitant Statin

Arm description:

One SC injection of each Alirocumab 75 mg and placebo Q2W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727, SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Investigational medicinal product name	Placebo (for Alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin

Arm description:

Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727, SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Investigational medicinal product name	Placebo (for Alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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	Placebo Q2W Without Concomitant Statin

Arm description:

Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) without stable statin therapy for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (for Alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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 Q2W/Up 150 mg Q2W Without Concomitant Statin

Arm description:

One SC injection of each Alirocumab 75 mg and placebo Q2W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.

Arm type	Experimental

Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727, SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

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

Investigational medicinal product name	Placebo (for Alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin

Arm description:

Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727, SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Physician decision	-	2	1
Related to IMP administration	-	-	-
Randomized and not treated	-	-	-
Adverse event	13	4	17
Subject moved	2	-	1
Other than specified	2	3	5
Poor compliance to protocol	5	3	8

Number of subjects in period 1	Placebo Q2W Without Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Started	73	37	146
Treated	72	37	146
Completed 24 Weeks Treatment Period	58	31	120
Completed	53	29	105
Not completed	20	8	41
Consent withdrawn by subject	1	-	5
Physician decision	1	-	-
Related to IMP administration	-	-	2
Randomized and not treated	1	-	-
Adverse event	4	3	14
Subject moved	1	-	3
Other than specified	12	4	11
Poor compliance to protocol	-	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W with Concomitant Statin
Reporting group description: Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) with stable statin therapy for 48 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin
Reporting group description: One SC injection of each Alirocumab 75 mg and placebo Q2W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Reporting group description: Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Placebo Q2W Without Concomitant Statin
Reporting group description: Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) without stable statin therapy for 48 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin
Reporting group description: One SC injection of each Alirocumab 75 mg and placebo Q2W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Reporting group description: Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	

Reporting group values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects	157	78	312
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.6	60.7	61.6
standard deviation	± 9.7	± 9.1	± 10
Gender categorical Units: Subjects			
Female	56	27	122

Male	101	51	190

Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol High density lipoprotein cholesterol [Triglyceride/5])			
Units: mg/dL			
arithmetic mean	112.1	114.9	112.4
standard deviation	± 37.3	± 36	± 32.8
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	2.903	2.977	2.912
standard deviation	± 0.965	± 0.933	± 0.85

Reporting group values	Placebo Q2W Without Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects	73	37	146
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.4	59.3	59.2
standard deviation	± 10.2	± 11.3	± 10.8
Gender categorical			
Units: Subjects			
Female	33	23	80
Male	40	14	66
Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol High density lipoprotein cholesterol [Triglyceride/5])			
Units: mg/dL			
arithmetic mean	131	148.4	146.1
standard deviation	± 30.4	± 36.8	± 33.5
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	3.392	3.842	3.785
standard deviation	± 0.787	± 0.953	± 0.868

Reporting group values	Total		
Number of subjects	803		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	341		

Male	462		

Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol High density lipoprotein cholesterol [Triglyceride/5])			
Units: mg/dL arithmetic mean standard deviation	- -		
Calculated LDL-C in mmol/L Units: mmol/L arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo Q2W with Concomitant Statin
Reporting group description:	
Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) with stable statin therapy for 48 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin
Reporting group description:	
One SC injection of each Alirocumab 75 mg and placebo Q2W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Reporting group description:	
Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W with stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Placebo Q2W Without Concomitant Statin
Reporting group description:	
Two Subcutaneous (SC) injections of placebo (for alirocumab) every two weeks (Q2W) without stable statin therapy for 48 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin
Reporting group description:	
One SC injection of each Alirocumab 75 mg and placebo Q2W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Reporting group description:	
Two SC injections of Alirocumab 150 mg every 4 weeks (Q4W) alternating with two SC injections of placebo Q4W without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg every two weeks (Q2W) from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	

Primary: Percent Change From Baseline in Calculated LDL-C in Subjects Receiving Concomitant Statin Therapy - Intent-to-Treat (ITT Analysis)

End point title	Percent Change From Baseline in Calculated LDL-C in Subjects Receiving Concomitant Statin Therapy - Intent-to-Treat (ITT Analysis)[1]
End point description:	
Adjusted least squares (LS) means and standard errors at Week 24 and at averaged Week 21 to 24 were obtained from a mixed effect model with repeated measures (MMRM) model 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 this model (ITT analysis). ITT population (subjects with concomitant statin therapy): all randomized subjects who received concomitant statin therapy, with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment. Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Primary

End point timeframe:

From Baseline to Week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is referring to only the 3 arms in which subjects were receiving concomitant statin therapy

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	76	308	
Units: Percent change				
least squares mean (standard error)				
At Week 24	-0.1 (± 2.3)	-51.6 (± 3.3)	-58.8 (± 1.6)	
At averaged Week 21 to 24	-0.8 (± 2)	-57.9 (± 2.8)	-65.8 (± 1.4)	

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mg Q4W/150mg Q2W: At Wk 24
Statistical analysis description:	
Alirocumab 300 mg group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-58.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-65
upper limit	-52.4

Notes:

[2] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mg Q4W/150mg Q2W: Wk 21-24
Statistical analysis description:	
Alirocumab 300 mg group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin

Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-65
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-70.4
upper limit	-59.5

Notes:

[3] - Threshold for significance ≤ 0.025.

Primary: Percent Change From Baseline in Calculated LDL-C in Subjects Not Receiving Concomitant Statin Therapy – ITT Analysis

End point title	Percent Change From Baseline in Calculated LDL-C in Subjects Not Receiving Concomitant Statin Therapy – ITT Analysis[4]

End point description:

Adjusted LS means and standard errors at Week 24 and at averaged Week 21 to 24 from MMRM including available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population (subjects without concomitant statin therapy): all randomized subjects who did not receive concomitant statin therapy, with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment. Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Primary

End point timeframe:

From Baseline to Week 24

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is referring to only the 3 arms in which subjects were not receiving concomitant statin therapy

End point values	Placebo Q2W Without Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	37	144	
Units: Percent change				
least squares mean (standard error)				
At Week 24	-0.3 (± 2.7)	-50.2 (± 3.7)	-52.7 (± 1.9)	
At averaged Week 21 to 24	-1.6 (± 2.6)	-54 (± 3.6)	-56.9 (± 1.8)	

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mg Q4W/150mg Q2W: At Wk 24

Statistical analysis description:	
Alirocumab 300 mg group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-52.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-59.8
upper limit	-45

Notes:

[5] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mg Q4W/150mg Q2W: Wk 21-24
Statistical analysis description:	
Alirocumab 300 mg group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-55.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-62.3
upper limit	-48.1

Notes:

[6] - Threshold for significance ≤ 0.025.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection) (on-treatment analysis). Modified ITT (mITT) population (subjects with or without concomitant statin therapy): all randomized and treated subjects who did not receive concomitant statin therapy, with one baseline and at least one post-baseline calculated LDL-C value on-treatment. Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	75	302	70
Units: percent change				
least squares mean (standard error)	-0.3 (± 2.1)	-55.1 (± 3)	-62.3 (± 1.5)	-0.4 (± 2)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	141		
Units: percent change				
least squares mean (standard error)	-54.6 (± 2.8)	-59.4 (± 1.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level.

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-59
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-64.6
upper limit	-53.4

Notes:

[7] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-62
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-67.7
upper limit	-56.2

Notes:

[8] - Threshold for significance ≤ 0.025.

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

End point title	Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis
End point description:	
Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	1.1 (± 2.2)	-45.3 (± 3.1)	-55.3 (± 1.5)	0.3 (± 2.1)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-51.8 (± 2.9)	-58.4 (± 1.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis

-58.7

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-62.3
upper limit	-50.3

Notes:

[10] - Threshold for significance ≤ 0.025.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 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). mITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	75	302	70
Units: percent change				
least squares mean (standard error)	1.4 (± 1.9)	-47.3 (± 2.8)	-58 (± 1.4)	-0.5 (± 2)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	141		
Units: percent change				
least squares mean (standard error)	-53.9 (± 2.7)	-60 (± 1.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-59.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-65
upper limit	-54.1

Notes:

[11] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-59.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-64.8
upper limit	-54

Notes:

[12] - Threshold for significance ≤ 0.025.

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 of the ITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline Apo B value on- or off-treatment (Apo B ITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary
End point timeframe: From Baseline to Week 24	

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	146	75	292	71
Units: percent change				
least squares mean (standard error)	3.1 (± 1.8)	-36.7 (± 2.6)	-45.1 (± 1.3)	-0.7 (± 2.3)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	138		
Units: percent change				
least squares mean (standard error)	-39 (± 3.3)	-40.2 (± 1.6)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description: Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-45.8
upper limit	-33.1

Notes:

[13] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-48.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-53.2
upper limit	-43.2

Notes:

[14] - Threshold for significance ≤ 0.025.

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

End point title	Percent Change From Baseline in Apo B at Week 24 - On-Treatment Analysis
End point description:	
Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). Subjects of mITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline Apo-B value on-treatment (Apo B mITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	142	74	286	70
Units: percent change				
least squares mean (standard error)	3.1 (± 1.7)	-38.3 (± 2.5)	-47.2 (± 1.2)	-0.3 (± 2)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	141		
Units: percent change				
least squares mean (standard error)	-42 (± 2.7)	-44.8 (± 1.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-49.9
upper limit	-39.1

Notes:

[15] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-50.3

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-55
upper limit	-45.6

Notes:

[16] - Threshold for significance ≤ 0.025.

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 of the ITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment (non-HDL-C ITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	0.3 (± 1.9)	-41.6 (± 2.7)	-49.7 (± 1.3)	-0.3 (± 2.5)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-43.6 (± 3.4)	-43.3 (± 1.7)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-43
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-49.9
upper limit	-36.2

Notes:

[17] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-50
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-55.3
upper limit	-44.8

Notes:

[18] - Threshold for significance ≤ 0.025.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). Subjects of the mITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline non-HDL-C value on-treatment (non-HDL-C mITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was

performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	75	302	70
Units: percent change				
least squares mean (standard error)	0.2 (± 1.8)	-44.4 (± 2.5)	-52.6 (± 1.2)	0.1 (± 2.1)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	141		
Units: percent change				
least squares mean (standard error)	-47.2 (± 2.8)	-48.9 (± 1.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-49
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-54.8
upper limit	-43.3

Notes:

[19] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-52.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-57.6
upper limit	-47.9

Notes:

[20] - Threshold for significance ≤ 0.025.

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 of the ITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline Total-C value on- or off-treatment (Total-C ITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	-0.8 (± 1.4)	-30 (± 2)	-35.8 (± 1)	-1.9 (± 1.9)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-32.5 (± 2.6)	-33.3 (± 1.3)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-36.6
upper limit	-26.3

Notes:

[21] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-38.9
upper limit	-31.1

Notes:

[22] - Threshold for significance ≤ 0.025.

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

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 (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was

Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-49
upper limit	-39.2

Notes:

[23] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-49.7
upper limit	-39.9

Notes:

[24] - Threshold for significance ≤ 0.025.

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 (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	0.6 (± 1.9)	-37.4 (± 2.7)	-46.5 (± 1.3)	-0.4 (± 1.8)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-45.8 (± 2.5)	-49.9 (± 1.3)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-49.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-54.5
upper limit	-44.6

Notes:

[25] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-47.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-52.2
upper limit	-42

Notes:

[26] - Threshold for significance ≤ 0.025.

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 (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 24	

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	-0.1 (± 1.3)	-26.5 (± 1.9)	-32.9 (± 1)	-1 (± 1.4)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-33.4 (± 2)	-37.4 (± 1)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-36.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-40.4
upper limit	-32.4

Notes:

[27] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.8

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-36.5
upper limit	-29.1

Notes:

[28] - Threshold for significance ≤ 0.025.

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

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

End point description:

Very high CV risk: history of documented coronary heart disease (CHD) or CHD risk equivalent. High CV risk: calculated 10-year fatal CVD risk score ≥5%, moderate chronic kidney disease, type 1/type 2 diabetes mellitus (DM) without target organ damage, or heFH not meeting definition of very high risk. Moderate CV risk: calculated 10-year fatal CVD risk score ≥1 &<5%. CHD risk equivalent: peripheral arterial disease, ischemic stroke, transient ischemic attack, abdominal aortic aneurysm, carotid artery(CA)occlusion>50%, carotid endarterectomy/CA stent procedure, renal artery stenosis/stent procedure, type 1/type 2 DM with target organ damage. Adjusted percentages at Week 24 obtained from 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 included in imputation model. ITT population (subjects with or without concomitant statin therapy).

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percentage of subjects				
number (not applicable)	22.2	82.5	85.2	9.4

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percentage of subjects				
number (not applicable)	84.9	78.9		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by logistic regression model.	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	68
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	20.9
upper limit	221

Notes:

[29] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used multiple imputation approach followed by logistic regression model.	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	25.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.7
upper limit	47.8

Notes:

[30] - Threshold for significance ≤ 0.025.

Secondary: Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL(1.81 mmol/L) or Moderate 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 Moderate 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 from 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). mITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	75	302	70
Units: percentage of subjects				
number (not applicable)	22.5	86.4	89.5	11.3

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	141		
Units: percentage of subjects				
number (not applicable)	93	88.6		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by logistic regression model.

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	280.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	56.7
upper limit	1385.7

Notes:

[31] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used multiple imputation approach followed by logistic regression model.

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	41.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	20.3
upper limit	83.8

Notes:

[32] - Threshold for significance ≤ 0.025.

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 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 population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percentage of subjects				
number (not applicable)	10.9	74.4	80.4	3.3

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percentage of subjects				
number (not applicable)	57.7	62		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by logistic regression model.	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	90.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	16.5
upper limit	498.3

Notes:

[33] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used multiple imputation approach followed by logistic regression model.

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	49.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	23.4
upper limit	104.4

Notes:

[34] - Threshold for significance ≤ 0.025.

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 from multiple imputation approach model including available post-baseline data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	75	302	70
Units: percentage of subjects				
number (not applicable)	10.8	77.4	84.8	2.1

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W	Alirocumab 300 mg Q4W/Up 150 mg Q2W		

Without

Notes:

[36] - Threshold for significance ≤ 0.025.

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 followed by robust regression 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 population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
arithmetic mean (standard error)	9.8 (± 2.4)	-16.9 (± 3.3)	-19.3 (± 1.6)	6.4 (± 3.4)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
arithmetic mean (standard error)	-14 (± 4.8)	-21.3 (± 2.4)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin v Placebo Q2W Without Concomitant Statin

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [37]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-27.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-37
upper limit	-18.3

Notes:

[37] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [38]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-29.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-35.5
upper limit	-22.7

Notes:

[38] - Threshold for significance ≤ 0.025.

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

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis

End point description:

Adjusted means and standard errors at Week 12 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
arithmetic mean (standard error)	7 (± 2.3)	-12.4 (± 3.2)	-19.6 (± 1.6)	-5.5 (± 3.3)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
arithmetic mean (standard error)	-26.9 (± 4.7)	-28.9 (± 2.3)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.	
Comparison groups	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin v Placebo Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-23.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-32.4
upper limit	-14.5

Notes:

[39] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [40]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-26.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-32.8
upper limit	-20.4

Notes:

[40] - Threshold for significance ≤ 0.025.

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 of the ITT population (with or without concomitant statin therapy) with one baseline and at least one post-baseline HDL-C value on- or off-treatment (HDL-C ITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	-1.5 (± 1.2)	6 (± 1.7)	3.6 (± 0.8)	-5.3 (± 1.7)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W	Alirocumab 300 mg Q4W/Up 150 mg Q2W		

	Without Concomitant Statin	Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	-0.1 (± 2.4)	2.5 (± 1.2)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [41]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	7.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	3.1
upper limit	12.6

Notes:

[41] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [42]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.9
upper limit	8.4

Notes:

[42] - Threshold for significance ≤ 0.025.

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 (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
least squares mean (standard error)	0.4 (± 1.2)	7.6 (± 1.8)	5.7 (± 0.9)	-0.9 (± 1.6)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
least squares mean (standard error)	2.5 (± 2.2)	6 (± 1.1)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [43]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	6.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	2.6
upper limit	11.1

Notes:

[43] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [44]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	5.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.8
upper limit	8.7

Notes:

[44] - Threshold for significance ≤ 0.025.

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

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

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
arithmetic mean (standard error)	-0.1 (± 2.4)	-6.7 (± 3.3)	-15.2 (± 1.6)	-1.5 (± 3.4)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
arithmetic mean (standard error)	-9.8 (± 4.9)	-13.4 (± 2.5)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.	
Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042 [45]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-11.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-21.3
upper limit	-2.6

Notes:

[45] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used multiple imputation approach followed by a robust regression model.

Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-15.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-21.5
upper limit	-8.6

Notes:

[46] - Threshold for significance ≤ 0.025.

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

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

End point description:

Adjusted means and standard errors at Week 12 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156	76	308	71
Units: percent change				
arithmetic mean (standard error)	0.5 (± 2.4)	-7.3 (± 3.5)	-13.1 (± 1.7)	1.8 (± 3.2)

End point values	Alirocumab 75 mg Q2W/Up	Alirocumab 300 mg Q4W/Up		

	150 mg Q2W Without Concomitant Statin	150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	144		
Units: percent change				
arithmetic mean (standard error)	-18.3 (± 4.6)	-12.3 (± 2.3)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Placebo Q2W Without Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [47]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-14.1
Confidence interval	
level	Other: 97.5 %
	2-sided
lower limit	-22.9
upper limit	-5.2

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-20.3
upper limit	-6.9

Notes:

[48] - Threshold for significance ≤ 0.025.

Secondary: Percent Change From Baseline in Apo A1 at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Apo A1 at Week 24 - 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. Subjects of the ITT population (subjects with or without concomitant statin therapy) with one baseline and at least one post-baseline Apo A1 value on- or off-treatment (Apo A1 ITT population). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	146	75	292	71
Units: percent change				
least squares mean (standard error)	2.9 (± 1)	6.5 (± 1.4)	5.5 (± 0.7)	-1.4 (± 1.3)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	138		
Units: percent change				
least squares mean (standard error)	3.1 (± 1.9)	5.2 (± 0.9)		

Statistical analyses

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin v Placebo Q2W Without Concomitant Statin
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	6.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	3
upper limit	10.2

Notes:

[49] - Threshold for significance ≤ 0.025.

Statistical analysis title	Placebo v Alirocumab 300mgQ4W/Up 150mgQ2W + Statin
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).	
Comparison groups	Placebo Q2W with Concomitant Statin v Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0306 [50]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.1
upper limit	5.4

Notes:

[50] - Threshold for significance ≤ 0.025.

Secondary: Percent Change From Baseline in Apo A1 at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Apo A1 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 A1 ITT population (subjects with or without concomitant statin therapy). Alirocumab 75 mg Q2W arm (calibrator arm) was included only to facilitate comparison of results of this study with the results of other studies that used an alirocumab 75 mg Q2W regimen. Hence no statistical comparison was performed for this arm.	
End point type	Secondary

End point timeframe:
From Baseline to Week 24

End point values	Placebo Q2W with Concomitant Statin	Alirocumab 75 mg Q2W/Up 150 mg Q2W with Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W with Concomitant Statin	Placebo Q2W Without Concomitant Statin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	146	75	292	71
Units: percent change				
least squares mean (standard error)	2.7 (± 1)	6.1 (± 1.4)	6 (± 0.7)	-1.8 (± 1.3)

End point values	Alirocumab 75 mg Q2W/Up 150 mg Q2W Without Concomitant Statin	Alirocumab 300 mg Q4W/Up 150 mg Q2W Without Concomitant Statin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	138		
Units: percent change				
least squares mean (standard error)	2.4 (± 1.8)	4.6 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 56 post-treatment follow-up visit) regardless of seriousness or relationship to investigational product.	
Adverse event reporting additional description:	
Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of study drug up to the last dose of study drug +70 days).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Two SC injections of placebo (for alirocumab) Q2W with or without stable statin therapy for 48 weeks.	
Reporting group title	Alirocumab 75 mg Q2W/Up 150 mg Q2W
Reporting group description:	
Two SC injections of Alirocumab 150 mg Q4W alternating with 2 SC injections of placebo Q4W with or without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	
Reporting group title	Alirocumab 300 mg Q4W/Up 150 mg Q2W
Reporting group description:	
Two SC injections of Alirocumab 300 mg Q4W alternating with two SC injections of placebo Q4W with or without stable statin therapy for 48 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) (for very high CV risk subjects) or ≥ 100 mg/dL (2.59 mmol/L) (for moderate and high CV risk subjects) at Week 8.	

Serious adverse events	Placebo Q2W	Alirocumab 75 mg Q2W/Up 150 mg Q2W	Alirocumab 300 mg Q4W/Up 150 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 229 (14.41%)	13 / 115 (11.30%)	53 / 458 (11.57%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenocortical carcinoma			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Fibrous histiocytoma			

subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal papillary-mucinous carcinoma of pancreas			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Deep vein thrombosis			

subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Hypertensive crisis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Hypotension			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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 compression			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery restenosis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Impaired healing			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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	1 / 229 (0.44%)	1 / 115 (0.87%)	4 / 458 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic mass			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Prostatic obstruction			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	3 / 229 (1.31%)	0 / 115 (0.00%)	3 / 458 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Nasal septum deviation			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Pulmonary embolism			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Pulmonary mass			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Tendon injury			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Meniscus injury			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Joint dislocation			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 229 (0.44%)	1 / 115 (0.87%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	2 / 229 (0.87%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Atrial fibrillation			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Cardiogenic shock			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Mitral valve incompetence			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Myocardial infarction			
subjects affected / exposed	3 / 229 (1.31%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Diverticular perforation			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Duodenal ulcer perforation			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiploic appendagitis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (0.00%)
occurrences causally related to treatment / all		0 / 1	0 / 0

subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Volvulus			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Nephrolithiasis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Renal failure			

subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Monarthritis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	0 / 458 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			

subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis c			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Gastroenteritis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	2 / 458 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 229 (0.44%)	2 / 115 (1.74%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			

Diabetic ketoacidosis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	0 / 458 (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
Dehydration			
subjects affected / exposed	1 / 229 (0.44%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 229 (0.00%)	0 / 115 (0.00%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 115 (0.87%)	1 / 458 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo Q2W	Alirocumab 75 mg Q2W/Up 150 mg Q2W	Alirocumab 300 mg Q4W/Up 150 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 229 (51.53%)	55 / 115 (47.83%)	229 / 458 (50.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 229 (5.24%)	4 / 115 (3.48%)	16 / 458 (3.49%)
occurrences (all)	12	4	19
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 229 (5.68%)	6 / 115 (5.22%)	29 / 458 (6.33%)
occurrences (all)	21	6	40
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	16 / 229 (6.99%)	10 / 115 (8.70%)	74 / 458 (16.16%)
occurrences (all)	22	28	126
Non-Cardiac chest pain			

subjects affected / exposed	5 / 229 (2.18%)	6 / 115 (5.22%)	7 / 458 (1.53%)
occurrences (all)	6	6	7
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 229 (6.55%)	7 / 115 (6.09%)	19 / 458 (4.15%)
occurrences (all)	16	8	20
Diarrhoea			
subjects affected / exposed	17 / 229 (7.42%)	4 / 115 (3.48%)	25 / 458 (5.46%)
occurrences (all)	19	6	28
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	13 / 229 (5.68%)	4 / 115 (3.48%)	10 / 458 (2.18%)
occurrences (all)	15	5	14
Back pain			
subjects affected / exposed	14 / 229 (6.11%)	3 / 115 (2.61%)	29 / 458 (6.33%)
occurrences (all)	14	3	30
Arthralgia			
subjects affected / exposed	15 / 229 (6.55%)	7 / 115 (6.09%)	29 / 458 (6.33%)
occurrences (all)	15	7	35
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 229 (7.86%)	10 / 115 (8.70%)	39 / 458 (8.52%)
occurrences (all)	29	11	46
Bronchitis			
subjects affected / exposed	12 / 229 (5.24%)	7 / 115 (6.09%)	19 / 458 (4.15%)
occurrences (all)	12	7	24
Urinary tract infection			
subjects affected / exposed	10 / 229 (4.37%)	7 / 115 (6.09%)	28 / 458 (6.11%)
occurrences (all)	12	7	31
Sinusitis			
subjects affected / exposed	11 / 229 (4.80%)	4 / 115 (3.48%)	28 / 458 (6.11%)
occurrences (all)	12	4	31
Upper respiratory tract infection			
subjects affected / exposed	18 / 229 (7.86%)	8 / 115 (6.96%)	41 / 458 (8.95%)
occurrences (all)	19	9	53

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2013	- The upper limit of LDL-C was changed from 190 mg/dL to 160 mg/dL for subjects at moderate CVD risk, for consistency with Adult Treatment Panel (ATP) III guidelines. - The term "statin inappropriate" was replaced with "statin intolerant", to ensure the appropriate study population was enrolled. A definition for statin intolerance had been added. - The definitions for moderate, high, and very high CVD risk were added for clarity.
26 August 2014	- Primary efficacy single endpoint within each concomitant statin therapy population was modified (i.e, subjects who received concomitant statin therapy and subjects who did not receive concomitant statin therapy) to co-primary (i.e, 2) efficacy endpoints. - Efficacy alpha level was not adjusted in this study for the 2 co-primary endpoints, since study was to be considered positive within a given concomitant statin population if statistical significance was met for both co-primary endpoints. - The primary efficacy analysis population was modified to ITT population for the primary and secondary efficacy endpoints, which included assessments both on- and off- study treatment through analysis period. - Statistical methodology for primary and secondary efficacy analysis endpoints was modified as follows: An MMRM was to be used for 2 co-primary endpoints and for other continuous secondary endpoints anticipated to have normally distributed data; For continuous endpoints expected to had non-normally distributed data, robust regression method was to be used to test treatment group differences and missing data was to be handled using multiple imputation approach; For binary endpoints, logistic regression method was to be used to test treatment group differences and missing data was to be handled using multiple imputation approach. - Specified further the sensitivity analyses that was to be performed on primary efficacy endpoint. - Primary and key secondary endpoints was also to be analyzed in mITT population to assess 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. - Clarified that LDL-C, measured and calculated, was to be performed at weeks 0 and 24.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported