# 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<br>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 |

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.

| **Number of subjects in period 1** | 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 |
|---|---|---|---|
| Started | 157 | 78 | 312 |
| Treated | 157 | 78 | 312 |
| Completed 24 Weeks Treatment Period | 137 | 68 | 285 |
| Completed | 129 | 65 | 272 |
| Not completed | 28 | 13 | 40 |
| Consent withdrawn by subject | 6 | 1 | 8 |

| | | | |
|---|---|---|---|
| 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<br>arithmetic mean<br>standard deviation | -<br> | | |
| Calculated LDL-C in mmol/L<br>Units: mmol/L<br>arithmetic mean<br>standard deviation | -<br> | | |

## 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 |
| Parameter estimate | LS Mean Difference |
| Point estimate | -58.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -64.5 |
| upper limit | -53 |

Notes:

[9] - 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 [10] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -56.3 |

| 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 |
|---|---|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo B ITT population (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) | 3.6 (± 1.8) | -33 (± 2.5) | -41.2 (± 1.3) | -2.3 (± 1.7) |

| 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) | -40.8 (± 2.5) | -46.4 (± 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 | 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 Concomitant Statin | Without Concomitant Statin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 37 | 141 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 61.7 | 70.4 | | |

## 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 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 [35] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 297.1 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 27.9 |
| upper limit | 3160.6 |

Notes:

[35] - 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 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 [36] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 77.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 34.1 |
| upper limit | 176.8 |

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 % |
| sides | 2-sided |
| lower limit | -22.9 |
| upper limit | -5.2 |

Notes:

[47] - 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 [48] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -13.6 |

| 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 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated umbilical hernia | | | |

| | | | |
|---|---|---|---|
| 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.<br>- 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.<br>- 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.<br>- 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.<br>- 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.<br>- 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.<br>- Specified further the sensitivity analyses that was to be performed on primary efficacy endpoint.<br>- 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).<br>- The list of key and other secondary efficacy endpoints and estimands (ITT estimand or on-treatment estimand) were adjusted.<br>- 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