# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Alirocumab in Patients with Primary Hypercholesterolemia Not Treated With a Statin

## Summary

| | |
|---|---|
| EudraCT number | 2013-002659-14 |
| Trial protocol | BE NL ES DK |
| Global end of trial date | 30 June 2017 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 15 July 2018 |
| First version publication date | 09 February 2017 |
| Version creation reason | • New data added to full data set<br>Addition of results covering the 2nd period of the study. |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | EFC13786 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02023879 |
| WHO universal trial number (UTN) | U1111-1146-3517 |
| Other trial identifiers | Study Name: ODYSSEY CHOICE II |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 15 December 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by a regimen including an Alirocumab starting dose of 150 mg every 4 weeks (Q4W) as add-on to non-statin lipid modifying background therapy or as monotherapy in comparison with placebo in subjects with primary hypercholesterolemia not treated with a statin.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

All subjects were to maintain a stable diet throughout the entire study duration, including the screening period. Subjects receiving background non-statin lipid modifying therapy (LMT) (ezetimibe or fenofibrate) had to continue their treatment without change (including dose) from screening through the end of 24-week double-blind (DB) treatment period barring exceptional circumstances.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 16 December 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 | Netherlands: 56 |
| Country: Number of subjects enrolled | Spain: 28 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Denmark: 21 |
| Country: Number of subjects enrolled | Australia: 12 |
| Country: Number of subjects enrolled | Canada: 27 |
| Country: Number of subjects enrolled | New Zealand: 6 |
| Country: Number of subjects enrolled | United States: 71 |
| Worldwide total number of subjects | 233 |
| EEA total number of subjects | 117 |

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) | 125 |
| From 65 to 84 years | 104 |
| 85 years and over | 4 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 43 centers in 8 countries. A total of 402 subjects were screened between December-2013 and May-2014, of whom 233 were randomized for double-blind (DB) treatment period and 169 were screen failures. Out of 233 randomized for DB period, 205 subjects entered the optional open-label (OL) extension period.

### Pre-assignment

Screening details:

Randomization was stratified by statin intolerant status and background therapy (non-statin lipid therapy vs diet). Randomization followed a 1:2:1 ratio for placebo, Alirocumab 75 mg and Alirocumab 150 mg instead of 1:1:2 as initially planned due to systematic error in treatment allocation algorithm discovered after all subjects were randomized.

### Period 1

| | |
|---|---|
| Period 1 title | Period 1: Double-blind Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Carer, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo Q2W |

Arm description:

Placebo (for Alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| | |
|---|---|
| **Arm title** | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) |

Arm description:

Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline.

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

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| | |
|---|---|
| **Arm title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W |

Arm description:

Alirocumab 150 mg SC injection Q4W alternating with placebo (for alirocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline.

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

Dosage and administration details:

1 ml subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| **Number of subjects in period 1** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W |
|---|---|---|---|
| Started | 58 | 116 | 59 |
| Treated | 58 | 115 | 58 |
| Completed | 54 | 107 | 50 |
| Not completed | 4 | 9 | 9 |
| Consent withdrawn by subject | 1 | - | 1 |
| Physician decision | - | 1 | - |
| Adverse events | 2 | 2 | 5 |
| Randomized but not treated | - | 1 | 1 |
| Other | 1 | 3 | 1 |
| Protocol deviation | - | 2 | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Period 2: Open Label Extension Treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Alirocumab 150 mg Q4W (after Placebo Q2W) |

Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Placebo (for Alirocumab) Q2W for 24 weeks. The alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

Dosage and administration details:

1 ml subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| | |
|---|---|
| **Arm title** | Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W) |

Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 75 mg Q2W/150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| | |
|---|---|
| **Arm title** | Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W) |

Arm description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 150 mg Q4W/ 150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

Dosage and administration details:

1 ml subcutaneous injection in the abdomen, thigh or outer area of the upper arm by self-injection or by another designated person using the auto-injector.

| **Number of subjects in period 2[1]** | Alirocumab 150 mg Q4W (after Placebo Q2W) | Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W) | Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W) |
|---|---|---|---|
| Started | 51 | 106 | 48 |
| Completed | 46 | 89 | 43 |
| Not completed | 5 | 17 | 5 |
| Other than specified above | 2 | 7 | 2 |
| Adverse event | 1 | 7 | 3 |
| Poor compliance to protocol | 1 | 1 | - |
| Subject Moved | 1 | 2 | - |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The open-label extension period was optional for subjects who completed the double-blind treatment period.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo Q2W |
| Reporting group description: | |
| Placebo (for Alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks. | |
| Reporting group title | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) |
| Reporting group description: | |
| Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline. | |
| Reporting group title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W |
| Reporting group description: | |
| Alirocumab 150 mg SC injection Q4W alternating with placebo (for alirocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline. | |

| **Reporting group values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W |
|---|---|---|---|
| Number of subjects | 58 | 116 | 59 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.1 | 62.5 | 64.2 |
| standard deviation | ± 10.7 | ± 9.9 | ± 10 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 27 | 47 | 29 |
| Male | 31 | 69 | 30 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 1 | 4 | 3 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| Black or African American | 1 | 3 | 1 |
| White | 56 | 108 | 55 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 7 | 4 |
| Not Hispanic or Latino | 57 | 109 | 54 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Calculated LDL-C in mg/dL | | | |
| Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol [Total-C] - High-Density Lipoprotein Cholesterol [HDL-C] - [Triglyceride/5]). | | | |
| Units: mg/dL | | | |

| | | | |
|---|---|---|---|
| arithmetic mean | 158.5 | 154.5 | 163.9 |
| standard deviation | ± 47.3 | ± 44.6 | ± 69.1 |
| Calculated LDL-C in mmol/L | | | |
| Units: mmol/L | | | |
| arithmetic mean | 4.106 | 4.002 | 4.245 |
| standard deviation | ± 1.226 | ± 1.154 | ± 1.789 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 233 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 103 | | |
| Male | 130 | | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 8 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Black or African American | 5 | | |
| White | 219 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 12 | | |
| Not Hispanic or Latino | 220 | | |
| Unknown or Not Reported | 1 | | |
| Calculated LDL-C in mg/dL | | | |
| Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol [Total-C] - High-Density Lipoprotein Cholesterol [HDL-C] - [Triglyceride/5]). | | | |
| Units: mg/dL | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Calculated LDL-C in mmol/L | | | |
| Units: mmol/L | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

## End points

### End points reporting groups

| Reporting group title | Placebo Q2W |
|---|---|

Reporting group description:

Placebo (for Alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable non-statin lipid modifying therapy (LMT) or diet alone for 24 weeks.

| Reporting group title | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) |
|---|---|

Reporting group description:

Alirocumab 75 mg SC injection Q2W added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline.

| Reporting group title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W |
|---|---|

Reporting group description:

Alirocumab 150 mg SC injection Q4W alternating with placebo (for alirocumab) QW4 added to stable non-statin LMT or diet alone for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when targeted low-density lipoprotein cholesterol (LDL-C) levels at Week 8 were not achieved i.e. LDL-C ≥70 mg/dL (1.81 mmol/L) or ≥100 mg/dL (2.59 mmol/L) depending on cardiovascular risk or <30% LDL-C reduction from baseline.

| Reporting group title | Alirocumab 150 mg Q4W (after Placebo Q2W) |
|---|---|

Reporting group description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Placebo (for Alirocumab) Q2W for 24 weeks. The alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

| Reporting group title | Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W) |
|---|---|

Reporting group description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 75 mg Q2W/150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

| Reporting group title | Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W) |
|---|---|

Reporting group description:

Alirocumab 150 mg SC injection Q4W from Week 24 until second quarter 2017 or until the drug is commercially available in the country, whatever occurred first, in subjects who received Alirocumab 150 mg Q4W/ 150 mg Q2W for 24 weeks. Alirocumab dose could be either up-titrated to 150 mg Q2W from Week 36 or maintained according to the investigator judgement and LDL-C values. Subsequent down titration to 150 mg Q4W was allowed.

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

| End point title | Percent Change From Baseline in Calculated LDL-C at Week 24 Intent-to-Treat (ITT Analysis) |
|---|---|

End point description:

Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population that included all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment.

| End point type | Primary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 4.7 (± 2.3) | -53.5 (± 1.6) | -51.7 (± 2.3) | |

**Statistical analyses**

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

Alirocumab 150 mg Q4W/up to 150 mg Q2W was compared to placebo group using an appropriate contrast statement.

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [1] |
| Method | Mixed models analysis |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -56.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -62.9 |
| upper limit | -49.9 |

Notes:

[1] - Threshold for significance at 0.05 level.

**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 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 that included all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 5.1 (± 2.1) | -55.3 (± 1.5) | -54.6 (± 2.1) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [2] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -59.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -65.6 |
| upper limit | -53.8 |

Notes:

[2] - Threshold for significance at 0.05 level.

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.2 (± 2.5) | -50.8 (± 1.7) | -41.7 (± 2.4) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -44.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.8 |
| upper limit | -38.1 |

Notes:

[3] - Threshold for significance at 0.05 level.

**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.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.6 (± 2.3) | -51.5 (± 1.6) | -44.8 (± 2.3) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [4] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -48.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.8 |
| upper limit | -41.9 |

Notes:

[4] - Threshold for significance at 0.05 level.

**Secondary: Percent Change From Baseline in Calculated LDL-C to Averaged Weeks 9 to 12 - ITT- Analysis**

| End point title | Percent Change From Baseline in Calculated LDL-C to Averaged Weeks 9 to 12 - ITT- Analysis |
|---|---|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment and assigning a weight of 0.25 for Week 9, 10, 11 and 12 time points. ITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.2 (± 2) | -53.6 (± 1.4) | -52.3 (± 2) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [5] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -55.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -61.1 |
| upper limit | -49.8 |

Notes:

[5] - Threshold for significance at 0.05 level.

**Secondary: Percent Change From Baseline in Calculated LDL-C at Averaged Week 9 to 12 - On-Treatment Analysis**

| End point title | Percent Change From Baseline in Calculated LDL-C at Averaged Week 9 to 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) and assigning a weight of 0.25 for Week 9, 10, 11 and 12 time points. mITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.6 (± 1.9) | -54.1 (± 1.3) | -55 (± 1.9) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [6] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -58.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -63.8 |
| upper limit | -53.4 |

Notes:

[6] - Threshold for significance at 0.05 level.

**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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 112 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 7.5 (± 2.1) | -39.7 (± 1.5) | -38.9 (± 2.2) | |

### Statistical analyses

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -46.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -52.4 |
| upper limit | -40.4 |

Notes:

[7] - Threshold for significance at 0.05 level.

### 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 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. Number of subjects analyzed = subjects of the mITT population with available data at specified time-points.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 54 | 112 | 54 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 7.7 (± 2) | -41.2 (± 1.4) | -40.9 (± 2.1) | |

**Statistical analyses**

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [8] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -48.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.3 |
| upper limit | -42.8 |

Notes:

[8] - Threshold for significance at 0.05 level.

**Secondary: Percent Change From Baseline in Non-HDL-C at Week 24 - ITT Analysis**

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 4.8 (± 2.1) | -45.3 (± 1.5) | -44.2 (± 2.1) | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [9] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.9 |
| upper limit | -43.2 |

Notes:

[9] - Threshold for significance at 0.05 level.

### 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). mITT population.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 5 (± 1.9) | -46.9 (± 1.3) | -46.7 (± 1.9) | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [10] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -51.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -57.1 |
| upper limit | -46.4 |

Notes:

[10] - Threshold for significance at 0.05 level.

### Secondary: Percent Change From Baseline in Total-C at Week 24 - ITT Analysis

| End point title | Percent Change From Baseline in Total-C at Week 24 - ITT Analysis |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3 (± 1.6) | -34 (± 1.1) | -32.3 (± 1.6) | |

**Statistical analyses**

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [11] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -35.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.8 |
| upper limit | -30.8 |

Notes:

[11] - Threshold for significance at 0.05 level.

**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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 112 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 7 (± 2.2) | -38.4 (± 1.6) | -31.3 (± 2.2) | |

**Statistical analyses**

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [12] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -38.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -44.3 |
| upper limit | -32.1 |

Notes:

[12] - Threshold for significance at 0.05 level.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3 (± 2.2) | -43.4 (± 1.5) | -34.9 (± 2.2) | |

### Statistical analyses

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [13] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -37.9 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -43.9 |
| upper limit | -31.8 |

Notes:

[13] - Threshold for significance at 0.05 level.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 1.8 (± 1.6) | -32.6 (± 1.2) | -24.5 (± 1.6) | |

## Statistical analyses

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [14] |
| Method | Mixed models analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -26.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.9 |
| upper limit | -21.7 |

Notes:

[14] - Threshold for significance at 0.05 level.

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

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

End point description:

Moderate CV risk: 10-year fatal cardiovascular disease (CVD) risk Systemic Coronary Risk Evaluation (SCORE) ≥1 and <5%.

High CV risk: 10-year fatal CVD risk SCORE ≥5% or moderate chronic kidney disease or type 1 or type 2 diabetes mellitus without target organ damage or familial hypercholesterolemia.

Very high CV risk: history of documented coronary heart disease, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis, or renal artery stent procedure; or type 1 or type 2 diabetes mellitus with target organ damage.

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were included. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 1.8 | 70.3 | 63.9 | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

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 logistic regression model.

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [15] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 279.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 29.1 |
| upper limit | 2690.1 |

Notes:

[15] - Threshold for significance at 0.05 level.

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

End point description:

Adjusted percentages at Week 24 from multiple imputation approach including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 1.8 | 72.7 | 67.7 | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

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 | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [16] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 354.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 36.2 |
| upper limit | 3479.5 |

Notes:

[16] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted percentages at Week 24 from last observation carried forward (LOCF) approach including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 0 | 60 | 50 | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [17] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 126 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20 |
| upper limit | 9999 |

Notes:

[17] - Threshold for significance at 0.05 level. Confidence interval should be read as 20.0 to >9999.

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

| | |
|---|---|
| End point title | Percentage of Subjects Achieving 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 LOCF approach including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 115 | 57 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 0 | 61.7 | 50.9 | |

### Statistical analyses

| Statistical analysis title | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [18] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 141.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.2 |
| upper limit | 9999 |

Notes:

[18] - Threshold for significance at 0.05 level. Confidence interval should be read as 20.0 to >9999.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 4.1 (± 3.7) | -21.8 (± 2.6) | -15.5 (± 3.7) | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

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 robust regression model.

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 [19] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -19.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.8 |
| upper limit | -9.4 |

Notes:

[19] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted means and standard errors at Week 12 from a multiple imputation approach 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.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 2.2 (± 3.4) | -16.5 (± 2.4) | -5.7 (± 3.3) | |

### Statistical analyses

| **Statistical analysis title** | Alirocumab 150 mg Q4W/Up to 150 mg Q2W vs. Placebo |
|---|---|

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 robust regression model.

| | |
|---|---|
| Comparison groups | Alirocumab 150 mg Q4W/Up to 150 mg Q2W v Placebo Q2W |

| | |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0892 [20] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -7.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.1 |
| upper limit | 1.2 |

Notes:

[20] - Threshold for significance at 0.05 level.

## 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 including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | -2.4 (± 1.9) | 7.4 (± 1.4) | 7.7 (± 2) | |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | -0.8 (± 1.9) | 6.8 (± 1.3) | 8.6 (± 1.9) | |

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted means and standard errors at Week 24 from a 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.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 1.1 (± 3.8) | -10.6 (± 2.7) | -9.2 (± 3.9) | |

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted means and standard errors at Week 12 from a multiple imputation approach 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.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 115 | 58 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 2.1 (± 3.9) | -11.3 (± 2.7) | -3 (± 3.8) | |

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| **End point values** | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 112 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.4 (± 1.5) | 8.2 (± 1.1) | 10 (± 1.5) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis

| End point title | Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis |
|---|---|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on-or off-treatment. ITT population. Number of subjects analyzed = subjects of the ITT population with available data at specified time-points.

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo Q2W | Alirocumab 75 mg Q2W/Up to 150 mg Q2W (Calibrator) | Alirocumab 150 mg Q4W/Up to 150 mg Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 112 | 58 | |
| Units: percent change | | | | |
| least squares mean (standard error) | 2.6 (± 1.5) | 5.9 (± 1.1) | 7.6 (± 1.5) | |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 32, 36, 48, 72, 96, 120, 144, 168 On-Treatment Analysis in Open Label Extension Treatment Phase

| End point title | Percent Change From Baseline in Calculated LDL-C at Week 32, 36, 48, 72, 96, 120, 144, 168 On-Treatment Analysis in Open Label Extension Treatment Phase |
|---|---|

End point description:

Mean percent changes (and standard deviations) observed during the open-label extension period are provided. Open-label extension population included all randomized subjects who received at least one dose or part of dose of open-label IMP. Here, "n (number analyzed)" signifies the number of subjects evaluable for each specified time-point.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 32, 36, 48, 72, 96, 120, 144 and Week 168

| End point values | Alirocumab 150 mg Q4W (after Placebo Q2W) | Alirocumab 150 mg Q4W (after Alirocumab 75 Q2W/Up 150 Q2W) | Alirocumab 150 mg Q4W (after Alirocumab 150 Q4W/Up 150 Q2W) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 51 | 106 | 48 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 32 (n=48, 98, 45) | -37.3 (± 18.8) | -41.1 (± 21.2) | -46.9 (± 13.3) | |
| Week 36 (n=48, 96, 46) | -36.1 (± 22.0) | -39.2 (± 21.2) | -43.1 (± 13.7) | |
| Week 48 (n=47, 91, 44) | -46.5 (± 24.2) | -49.2 (± 18.7) | -48.7 (± 21.7) | |
| Week 72 (n=50, 94, 47) | -50.8 (± 20.6) | -53.7 (± 19.5) | -52.3 (± 21.3) | |
| Week 96 (n=48, 90, 44) | -49.8 (± 20.4) | -52.8 (± 19.6) | -46.8 (± 22.0) | |
| Week 120 (n=46, 81, 37) | -50.6 (± 20.9) | -53.7 (± 18.7) | -51.8 (± 24.1) | |
| Week 144 (n=38, 72, 29) | -52.7 (± 17.6) | -48.7 (± 23.7) | -49.4 (± 20.9) | |
| Week 168 (n=4, 13, 4) | -47.8 (± 24.2) | -66.2 (± 17.1) | -60.0 (± 4.6) | |

## 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 informed consent form up to study completion (up to 176 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs/deaths are treatment-emergent ie; AEs that developed/worsened and deaths that occurred 'on treatment'; from 1st dose up to last dose (active/placebo depending on Q2W/Q4W dosing) in DB period+70 days, truncated at the day before 1st dose in OL period for subjects entering in OL period; from 1st dose up to last dose in OL period+70 days.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo Q2W |

Reporting group description:

Subjects exposed to placebo SC injection Q2W added to stable non-statin LMT or diet alone (mean exposure of 23 weeks).

| | |
|---|---|
| Reporting group title | Alirocumab 75 mg Q2W/Up150 mg Q2W |

Reporting group description:

Subjects exposed to alirocumab 75 mg Q2W/up to 150 mg Q2W SC injection added to stable non-statin LMT or diet alone (mean exposure of 23 weeks).

| | |
|---|---|
| Reporting group title | Alirocumab 150 mg Q4W/Up150 mg Q2W |

Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W/up to 150 mg Q2W SC injection added to stable non-statin LMT or diet alone (mean exposure of 22 weeks).

| | |
|---|---|
| Reporting group title | Alirocumab 150 mg Q4W (After Placebo Q2W) |

Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 128 weeks) after having received Placebo Q2W for 24 weeks.

| | |
|---|---|
| Reporting group title | Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W) |

Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 117 weeks) after having received Alirocumab 75 mg Q2W/Up to 150 mg Q2W for 24 weeks.

| | |
|---|---|
| Reporting group title | Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W) |

Reporting group description:

Subjects exposed to alirocumab 150 mg Q4W SC injection added to stable non-statin LMT or diet alone (mean exposure of 119 weeks) after having received Alirocumab 150 mg Q4W/Up to 150 mg Q2W for 24 weeks.

| **Serious adverse events** | Placebo Q2W | Alirocumab 75 mg Q2W/Up150 mg Q2W | Alirocumab 150 mg Q4W/Up150 mg Q2W |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 7 / 115 (6.09%) | 7 / 58 (12.07%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from | | | |

| adverse events | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma Of Colon | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign Fallopian Tube Neoplasm | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Bladder Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast Cancer | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningioma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| 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 Squamous Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate Cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 115 (0.87%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Cancer | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic Shock | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Artery Occlusion | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Artery Stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| 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 | | | |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental Disorder | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide Attempt | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Craniocerebral Injury | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus Fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional Overdose | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw Fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple Fractures | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Post Procedural Haematoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius Fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib Fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road Traffic Accident | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal Fracture | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural Haematoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic Haemothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic Renal Injury | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular Pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina Pectoris | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Angina Unstable | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic Valve Stenosis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial Fibrillation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-Respiratory Arrest | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral Valve Incompetence | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Arachnoiditis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar Infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Essential Tremor | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxic-Ischaemic Encephalopathy | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple Sclerosis Relapse | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Haemorrhagic Anaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal Detachment | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Abdominal Wall Haematoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Faecaloma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Retroperitoneal Haematoma | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small Intestinal Obstruction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary Colic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Basedow's Disease | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal Chest Pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (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 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Rheumatoid Arthritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal Osteoarthritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis Bacterial | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device Related Infection | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (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 |
| Urinary Tract Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Alirocumab 150 mg Q4W (After Placebo Q2W) | Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W) | Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 51 (29.41%) | 28 / 106 (26.42%) | 14 / 48 (29.17%) |
| number of deaths (all causes) | 0 | 2 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma Of Colon | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 106 (1.89%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign Fallopian Tube Neoplasm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Breast Cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningioma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal Squamous Cell Carcinoma | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate Cancer | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 106 (1.89%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Cancer | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Vascular disorders** | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 106 (1.89%) | 0 / 48 (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 |
| Hypovolaemic Shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 Artery Occlusion | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Artery Stenosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 106 (1.89%) | 0 / 48 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Mental Disorder | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide Attempt | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Craniocerebral Injury | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Fall | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |

| | | | |
|---|---|---|---|
| Humerus Fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Intentional Overdose | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Jaw Fracture | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple Fractures | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post Procedural Haematoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Radius Fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Rib Fracture | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Road Traffic Accident | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Spinal Fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Subdural Haematoma | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic Haemothorax | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Traumatic Renal Injury | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 Pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 106 (2.83%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Angina Unstable | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic Valve Stenosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 2 / 106 (1.89%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-Respiratory Arrest | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 106 (1.89%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral Valve Incompetence | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial Infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Nervous system disorders | | | |
| Arachnoiditis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Cerebellar Infarction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Essential Tremor | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Hypoxic-Ischaemic Encephalopathy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Multiple Sclerosis Relapse | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 106 (1.89%) | 0 / 48 (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 |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 106 (2.83%) | 2 / 48 (4.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic Anaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Eye disorders | | | |
| Retinal Detachment | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Abdominal Pain Upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Wall Haematoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Constipation | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Retroperitoneal Haematoma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Small Intestinal Obstruction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary Colic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Endocrine disorders | | | |
| Basedow's Disease | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal Chest Pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Myalgia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| 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 | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid Arthritis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Spinal Osteoarthritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |
| Arthritis Bacterial | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 106 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device Related Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 106 (0.94%) | 0 / 48 (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 |
| Hepatitis E | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 106 (0.94%) | 2 / 48 (4.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 106 (0.00%) | 0 / 48 (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 |

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

| **Non-serious adverse events** | Placebo Q2W | Alirocumab 75 mg Q2W/Up150 mg Q2W | Alirocumab 150 mg Q4W/Up150 mg Q2W |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 58 (48.28%) | 61 / 115 (53.04%) | 29 / 58 (50.00%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 6 / 115 (5.22%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 1 / 115 (0.87%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 1 | 2 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dizziness | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 1 / 115 (0.87%) | 4 / 58 (6.90%) |
| occurrences (all) | 4 | 1 | 4 |
| Headache | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 10 / 115 (8.70%) | 5 / 58 (8.62%) |
| occurrences (all) | 5 | 10 | 5 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 5 / 115 (4.35%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 5 | 4 |
| Injection Site Reaction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 4 / 115 (3.48%) | 8 / 58 (13.79%) |
| occurrences (all) | 0 | 6 | 25 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 3 / 115 (2.61%) | 0 / 58 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 3 / 115 (2.61%) | 0 / 58 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 5 / 115 (4.35%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 5 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 6 / 115 (5.22%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 6 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 3 / 115 (2.61%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 4 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dry Skin | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 0 | 1 |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 1 | 3 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 115 (1.74%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 8 / 115 (6.96%) | 7 / 58 (12.07%) |
| occurrences (all) | 4 | 8 | 8 |
| Back Pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 5 / 115 (4.35%) | 2 / 58 (3.45%) |
| occurrences (all) | 0 | 5 | 2 |
| Muscle Spasms | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 9 / 115 (7.83%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 9 | 3 |
| Musculoskeletal Pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 3 / 115 (2.61%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 7 / 115 (6.09%) | 3 / 58 (5.17%) |
| occurrences (all) | 3 | 10 | 3 |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 115 (1.74%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pain In Extremity | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 4 / 115 (3.48%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 4 | 3 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Influenza | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 58 (0.00%) | 3 / 115 (2.61%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 3 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 115 (0.87%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 115 (0.87%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 4 / 115 (3.48%) | 3 / 58 (5.17%) |
| occurrences (all) | 5 | 4 | 5 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 4 / 115 (3.48%) | 4 / 58 (6.90%) |
| occurrences (all) | 1 | 4 | 4 |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 10 / 115 (8.70%) | 5 / 58 (8.62%) |
| occurrences (all) | 3 | 11 | 7 |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 115 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 115 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| **Non-serious adverse events** | Alirocumab 150 mg Q4W (After Placebo Q2W) | Alirocumab 150 mg Q4W (After Alirocumab 75 Q2W/Up150 Q2W) | Alirocumab 150 mg Q4W (After Alirocumab 150 Q4W/Up150 Q2W) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 51 (82.35%) | 71 / 106 (66.98%) | 31 / 48 (64.58%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 14 / 106 (13.21%) | 2 / 48 (4.17%) |
| occurrences (all) | 6 | 14 | 3 |
| Laceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 106 (2.83%) | 0 / 48 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 8 / 106 (7.55%) | 2 / 48 (4.17%) |
| occurrences (all) | 2 | 8 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 5 / 106 (4.72%) | 4 / 48 (8.33%) |
| occurrences (all) | 4 | 5 | 4 |
| Headache | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 6 / 106 (5.66%) | 4 / 48 (8.33%) |
| occurrences (all) | 4 | 8 | 4 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 7 / 106 (6.60%) | 3 / 48 (6.25%) |
| occurrences (all) | 3 | 7 | 3 |
| Injection Site Reaction | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 7 / 106 (6.60%) | 7 / 48 (14.58%) |
| occurrences (all) | 3 | 12 | 37 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 5 / 106 (4.72%) | 1 / 48 (2.08%) |
| occurrences (all) | 7 | 5 | 1 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 5 / 106 (4.72%) | 5 / 48 (10.42%) |
| occurrences (all) | 4 | 5 | 5 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 11 / 106 (10.38%) | 2 / 48 (4.17%) |
| occurrences (all) | 4 | 15 | 2 |
| Nausea | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 3 / 106 (2.83%) | 3 / 48 (6.25%) |
| occurrences (all) | 1 | 3 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 51 (17.65%) | 9 / 106 (8.49%) | 1 / 48 (2.08%) |
| occurrences (all) | 9 | 11 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Dry Skin | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 106 (2.83%) | 1 / 48 (2.08%) |
| occurrences (all) | 0 | 3 | 1 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 7 / 106 (6.60%) | 0 / 48 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 51 (15.69%) | 7 / 106 (6.60%) | 3 / 48 (6.25%) |
| occurrences (all) | 11 | 8 | 6 |
| Back Pain | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 10 / 106 (9.43%) | 7 / 48 (14.58%) |
| occurrences (all) | 4 | 10 | 10 |
| Muscle Spasms | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 4 / 106 (3.77%) | 1 / 48 (2.08%) |
| occurrences (all) | 6 | 4 | 1 |
| Musculoskeletal Pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 6 / 106 (5.66%) | 2 / 48 (4.17%) |
| occurrences (all) | 1 | 6 | 2 |
| Myalgia | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 6 / 106 (5.66%) | 1 / 48 (2.08%) |
| occurrences (all) | 8 | 7 | 2 |
| Neck Pain | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 106 (0.00%) | 0 / 48 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 8 / 51 (15.69%) | 7 / 106 (6.60%) | 3 / 48 (6.25%) |
| occurrences (all) | 9 | 10 | 3 |
| Pain In Extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 51 (3.92%) | 3 / 106 (2.83%) | 1 / 48 (2.08%) |
| occurrences (all) | 2 | 3 | 1 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 4 / 106 (3.77%) | 5 / 48 (10.42%) |
| occurrences (all) | 5 | 5 | 8 |
| Influenza | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 9 / 106 (8.49%) | 4 / 48 (8.33%) |
| occurrences (all) | 4 | 12 | 4 |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 1 / 106 (0.94%) | 0 / 48 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 3 / 106 (2.83%) | 1 / 48 (2.08%) |
| occurrences (all) | 3 | 3 | 3 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 8 / 106 (7.55%) | 4 / 48 (8.33%) |
| occurrences (all) | 11 | 9 | 4 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 7 / 106 (6.60%) | 5 / 48 (10.42%) |
| occurrences (all) | 4 | 11 | 5 |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 16 / 106 (15.09%) | 9 / 48 (18.75%) |
| occurrences (all) | 5 | 25 | 11 |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 5 / 51 (9.80%) | 5 / 106 (4.72%) | 1 / 48 (2.08%) |
| occurrences (all) | 9 | 7 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 106 (0.94%) | 3 / 48 (6.25%) |
| occurrences (all) | 1 | 1 | 3 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 October 2013 | -Changes were made to the exclusion criterion for consistency with the 2004 adult treatment panel (ATP) III guidelines. -Timing of the primary endpoint was changed (at Week 24, to be consistent with the rest of the phase 3 program). –Changes were made to the analysis of the primary and secondary endpoints (use of an ITT approach). -Added collection of measured LDL-C at Week 0 and Week 24. |
| 25 August 2014 | -Adjusted the list of key and other secondary efficacy endpoints and estimands (ITT estimand and on-treatment estimand). -Added time points (Week 9, Week 10 and Week 11) in the model for the primary efficacy analysis endpoint. -Specified sensitivity analyses to be performed on the primary efficacy endpoint. |
| 08 July 2015 | - Extended the duration of the open-label treatment period to Q2 2017 or until alirocumab was commercially available in the country.<br>- Added a follow-up phone call for safety assessments 10 weeks after last IMP administration. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The systematic randomization error was not anticipated to have an impact on the power of the study. The sample size to detect a difference in efficacy endpoints was reached (it was increased to obtain additional safety data) and blind was maintained.

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/27625344