



Clinical trial results:

A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 Versus Ezetimibe in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-004130-34 |
| Trial protocol | HU DK DE |
| Global end of trial date | |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 |
| This version publication date | 08 March 2016 |
| First version publication date | 06 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC11569 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01644188 |
| WHO universal trial number (UTN) | U1111-1121-4315 |
| Other trial identifiers | Study name: ODYSSEY COMBO 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, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, 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 | Interim |
| Date of interim/final analysis | 26 June 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 May 2014 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab (SAR236553/REGN727) as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe 10 mg after 24 weeks of treatment in subjects with hypercholesterolemia at high cardiovascular (CV) risk.

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 had to receive a statin at maximally tolerated dose (simvastatin, atorvastatin and rosuvastatin). Background statin therapy was not to be changed (including dose) at least 4 weeks prior to the screening visit and throughout the whole study duration barring exceptional circumstances.

Evidence for comparator: -

| | |
|-----------------------------------------------------------|----------------|
| Actual start date of recruitment | 09 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | Israel: 23 |
| Country: Number of subjects enrolled | Korea, Republic of: 42 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Hungary: 65 |
| Country: Number of subjects enrolled | Denmark: 100 |
| Country: Number of subjects enrolled | Russian Federation: 149 |
| Country: Number of subjects enrolled | South Africa: 92 |
| Country: Number of subjects enrolled | Ukraine: 6 |
| Country: Number of subjects enrolled | United States: 217 |
| Worldwide total number of subjects | 720 |
| EEA total number of subjects | 174 |

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) | 434 |
| From 65 to 84 years | 282 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 126 centers in 10 countries. Overall, 1112 subjects were screened between August 2012 and May 2013, 392 of whom were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction (MI) or ischemic stroke, intensity of statin treatment and geographical region. Assignment to arms was done centrally using Interactive Voice/Web Response System in 2:1 ratio (alirocumab: ezetimibe) after confirmation of selection criteria. 720 subjects were randomized

Period 1

| | |
|------------------------------|-------------------------------------------|
| Period 1 title | Up to primary completion (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Blinding implementation details:

Alirocumab and placebo for alirocumab were provided in identically matched auto-injectors and packaged identically.

Ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labeled with a double-blind label.

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Alirocumab 75/up to 150 mg Q2W |

Arm description:

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks.

Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥ 70 mg/dL (1.81 mmol/L) at Week 8.

| | |
|----------------------------------------|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo (for ezetimibe) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One over-encapsulated tablet once daily at approximately the same time of the day with or without food.

| | |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Alirocumab |
| Investigational medicinal product code | SAR236553, REGN727 |
| 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 | Ezetimibe 10 mg |
|------------------|-----------------|

Arm description:

Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104

weeks.

| | |
|----------------------------------------|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ezetimibe |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One over-encapsulated tablet once daily at approximately the same time of the day with or without food.

| | |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Placebo (alirocumab) |
| 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 | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg |
|------------------------------------------|---------------------------------------|------------------------|
| Started | 479 | 241 |
| Completed first 52-week treatment period | 408 | 208 |
| Treated | 479 | 241 |
| Completed | 0 | 0 |
| Not completed | 479 | 241 |
| Physician decision | 1 | 2 |
| Other than specified here | 15 | 8 |
| Consent withdrawn by subject | - | 1 |
| Adverse event | 36 | 13 |
| Treatment ongoing | 406 | 206 |
| Subject moved | 6 | 2 |
| Poor compliance to protocol | 13 | 7 |
| Related to Autoinjector Administration | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Alirocumab 75/up to 150 mg Q2W |
|-----------------------|--------------------------------|

Reporting group description:

Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks.
Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥ 70 mg/dL (1.81 mmol/L) at Week 8.

| | |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe 10 mg |
|-----------------------|-----------------|

Reporting group description:

Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks.

| Reporting group values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | Total |
|------------------------------------|--------------------------------|-----------------|-------|
| Number of subjects | 479 | 241 | 720 |
| Age categorical Units: Subjects | | | |

| | | | |
|------------------------------------------------------------------------------------|-----------------|-----------------|------------|
| Age continuous Units: years arithmetic mean standard deviation | 61.7 ± 9.4 | 61.3 ± 9.2 | - |
| Gender categorical Units: Subjects Female Male | 119 360 | 71 170 | 190 530 |
| Calculated LDL-C in mmol/L | | | |
| Calculated LDL-C from Friedewald formula. | | | |
| Units: mmol/L arithmetic mean standard deviation | 2.81 ± 0.945 | 2.71 ± 0.884 | - |
| Calculated LDL-C in mg/dL Units: mg/dL arithmetic mean standard deviation | 108.6 ± 36.5 | 104.6 ± 34.1 | - |

End points

End points reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title | Alirocumab 75/up to 150 mg Q2W |
| Reporting group description: Subcutaneous alirocumab 75 mg every 2 weeks (Q2W) and oral placebo for ezetimibe daily added to stable Lipid-Modifying Therapy (LMT) for 104 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C level ≥ 70 mg/dL (1.81 mmol/L) at Week 8. | |
| Reporting group title | Ezetimibe 10 mg |
| Reporting group description: Oral ezetimibe 10 mg daily and subcutaneous placebo for alirocumab Q2W added to stable LMT for 104 weeks. | |
| Subject analysis set title | Ezetimibe 10 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects exposed to Ezetimibe 10 mg added to stable LMT (mean exposure of 58 weeks). | |
| Subject analysis set title | Alirocumab 75 /up to 150 mg Q2W |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects exposed to Alirocumab 75 /up to 150 mg Q2W added to stable LMT (mean exposure of 58 weeks). | |

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 52 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment. | |
| End point type | Primary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -50.6 (\pm 1.4) | -20.7 (\pm 1.9) | | |

Statistical analyses

| | |
|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. Ezetimibe |
| Statistical analysis description: Alirocumab group was compared to ezetimibe group using an appropriate contrast statement. | |
| Comparison groups | Ezetimibe 10 mg v Alirocumab 75/up to 150 mg Q2W |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.4 |
| upper limit | -25.3 |

Notes:

[1] - Threshold for significance ≤ 0.05

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

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 24 - On-treatment Analysis |
| End point description: Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis). Modified ITT population (mITT): 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 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 464 | 235 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -52.4 (\pm 1.3) | -21.8 (\pm 1.8) | | |

Statistical analyses

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| 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 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 699 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -30.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.9 |
| upper limit | -26.2 |

Notes:

[2] - Threshold for significance ≤ 0.05

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 a MMRM including all available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment (ITT analysis). ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -51.2 (\pm 1.3) | -21.8 (\pm 1.8) | | |

Statistical analyses

| | |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |

| | |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.7 |
| upper limit | -25.1 |

Notes:

[3] - Threshold for significance ≤ 0.05

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 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis). mITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 464 | 235 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -52.4 (\pm 1.2) | -22.7 (\pm 1.7) | | |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

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

| | |
|-----------------------------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 699 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.8 |
| upper limit | -25.6 |

Notes:

[4] - Threshold for significance <0.05

Secondary: Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24 - ITT analysis

| | |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24 - ITT analysis |
|-----------------|------------------------------------------------------------------------------------|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 452 | 228 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -40.7 (± 1.1) | -18.3 (± 1.5) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-----------------------------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 680 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26 |
| upper limit | -18.8 |

Notes:

[5] - Threshold for significance ≤ 0.05

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 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline Apo B value on-treatment. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 442 | 221 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -42.1 (± 1) | -19.1 (± 1.4) | | |

Statistical analyses

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.5 |
| upper limit | -19.6 |

Notes:

[6] - Threshold for significance ≤ 0.05

Secondary: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 24 - ITT Analysis

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 24 - ITT Analysis |
| End point description: Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -42.1 (± 1.2) | -19.2 (± 1.7) | | |

Statistical analyses

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.9 |
| upper limit | -18.9 |

Notes:

[7] - Threshold for significance ≤0.05.

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 52 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline | |

Non-HDL-C value on-treatment.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline up to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 464 | 235 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -43.7 (\pm 1.1) | -20.2 (\pm 1.6) | | |

Statistical analyses

| | |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 699 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -23.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.2 |
| upper limit | -19.7 |

Notes:

[8] - Threshold for significance ≤ 0.05

Secondary: Percent Change From Baseline in Total Cholesterol (TC) at Week 24 - ITT Analysis

| | |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Total Cholesterol (TC) at Week 24 - ITT Analysis |
|-----------------|----------------------------------------------------------------------------------|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline TC value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -29.3 (\pm 0.9) | -14.6 (\pm 1.2) | | |

Statistical analyses

| Statistical analysis title | Alirocumab vs. ezetimibe |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[9] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -14.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.7 |
| upper limit | -11.7 |

Notes:

[9] - Threshold for significance ≤ 0.05 .

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

| End point title | Percent Change From Baseline in Apo-B at Week 12 - ITT analysis |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point description: | |
| Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. | |
| Apo-B ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 452 | 228 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -39.7 (± 1) | -17.2 (± 1.3) | | |

Statistical analyses

| Statistical analysis title | Alirocumab vs. ezetimibe |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 680 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.7 |
| upper limit | -19.2 |

Notes:

[10] - Threshold for significance ≤ 0.05 .

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

| End point title | Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point description: | |
| Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Non-HDL-C ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -42.6 (± 1.1) | -20.6 (± 1.5) | | |

Statistical analyses

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[11] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.6 |
| upper limit | -18.3 |

Notes:

[11] - Threshold for significance ≤ 0.05

Secondary: Percent Change From Baseline in Total Cholesterol (TC) at Week 12 - ITT Analysis

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Total Cholesterol (TC) at Week 12 - ITT Analysis |
| End point description: Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. TC ITT population. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -29.4 (\pm 0.8) | -15.1 (\pm 1.1) | | |

Statistical analyses

| | |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -14.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.1 |
| upper limit | -11.6 |

Notes:

[12] - Threshold for significance ≤ 0.05

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis |
| End point description: | |
| Adjusted LS means and standard errors at Week 52 from a MMRM model including all available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment (ITT analysis). ITT population. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 52 | |

| | | | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -49.5 (\pm 1.5) | -18.3 (\pm 2.1) | | |

Statistical analyses

| | |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). | |
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |

| | |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[13] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -31.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.3 |
| upper limit | -26.1 |

Notes:

[13] - Threshold for significance ≤ 0.05

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 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from week 4 to week 52 regardless of status on- or off-treatment were included in the imputation model. ITT population.

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

End point timeframe:

Up to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 77 | 45.6 | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--------------------------------------------------|

| | |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[14] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.7 |
| upper limit | 7.9 |

Notes:

[14] - Threshold for significance ≤ 0.05

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 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from week 4 to week 52 i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first. mITT population.

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

End point timeframe:

Up to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 464 | 235 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 78.9 | 47.4 | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--------------------------------------------------|

| | |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 699 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[15] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.9 |
| upper limit | 8.8 |

Notes:

[15] - Threshold for significance ≤ 0.05

Secondary: Percent Change From Baseline in Lipoprotein(a) at Week 24 - ITT analysis

| | |
|-----------------|--------------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Lipoprotein(a) at Week 24 - ITT analysis |
|-----------------|--------------------------------------------------------------------------|

End point description:

Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population.

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

End point timeframe:

From baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|----------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -27.8 (\pm 1.4) | -6.1 (\pm 2) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--------------------------------------------------|

| | |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[16] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -21.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.4 |
| upper limit | -17 |

Notes:

[16] - Threshold for significance ≤ 0.05

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-----------------------------------------|--------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard deviation) | 8.6 (\pm 0.8) | 0.5 (\pm 1.1) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-----------------------------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[17] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 8.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.4 |
| upper limit | 10.7 |

Notes:

[17] - Threshold for significance ≤ 0.05

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

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

End point description:

Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Subjects analyzed: subjects of the ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|----------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -13 (\pm 1.5) | -12.8 (\pm 2) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Alirocumab vs. ezetimibe |
|----------------------------|--------------------------|

Statistical analysis description:

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

| | |
|-----------------------------------------|--------------------------------------------------|
| Comparison groups | Alirocumab 75/up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 707 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9117 ^[18] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.1 |
| upper limit | 4.6 |

Notes:

[18] - Threshold for significance ≤ 0.05

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo A-1 value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 452 | 228 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 5 (\pm 0.6) | -1.3 (\pm 0.8) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted means and standard errors at Week 12 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.

Lipoprotein(a) ITT population.

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

End point timeframe:

From Baseline to Week 12

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|----------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -22.1 (± 1.2) | 1.1 (± 1.7) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
HDL-C ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 8.7 (± 0.7) | 2.8 (± 1) | | |

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 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment.
Fasting Triglycerides ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|----------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -13 (\pm 1.5) | -12.8 (\pm 2) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| End point title | Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis |
| End point description: Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo A-1 ITT population. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | | |
|-------------------------------------|--------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 240 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 1.5 (\pm 0.5) | -2.9 (\pm 0.7) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the primary completion date regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during 'the treatment-emergent period' (from the first dose of double-blind IMP administration [capsule or injection, whichever came first] up the day of the last double-blind IMP injection + 70 days).

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Alirocumab 75/up to 150 mg Q2W |
|-----------------------|--------------------------------|

Reporting group description:

Subjects exposed to Alirocumab 75/up to 150 mg Q2W added to stable LMT (mean exposition of 58 weeks).

| | |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe 10 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects exposed to Ezetimibe 10 mg added to stable LMT (mean exposition of 58 weeks).

| Serious adverse events | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | |
|---------------------------------------------------------------------|--------------------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 90 / 479 (18.79%) | 43 / 241 (17.84%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Chronic Lymphocytic Leukaemia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate Cancer | | | |
| subjects affected / exposed | 3 / 479 (0.63%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal Carcinoma | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Small Cell Lung Cancer Stage Iiia | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Stromal Tumour | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant Melanoma | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung Neoplasm Malignant | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Small Cell Lung Cancer | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous Cell Carcinoma Of Lung | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Femoral Artery Occlusion | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Arterial Occlusive Disease | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Artery Aneurysm | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Sudden Cardiac Death | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest Pain | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden Death | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 3 / 479 (0.63%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional State | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed Suicide | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Bacterial Test Positive | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fibula Fracture | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Artery Restenosis | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle Fracture | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Contusion | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib Fracture | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis Fracture | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip Fracture | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple Fractures | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional Hernia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella Fracture | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 10 / 479 (2.09%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Unstable | | | |
| subjects affected / exposed | 8 / 479 (1.67%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Pectoris | | | |
| subjects affected / exposed | 8 / 479 (1.67%) | 6 / 241 (2.49%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular Block | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 4 / 479 (0.84%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis Coronary Artery | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Arrest | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrioventricular Block Second Degree | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular Block Complete | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Flutter | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Defect Conduction Intraventricular | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial Infarction | | | |
| subjects affected / exposed | 3 / 479 (0.63%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Silent Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular Extrasystoles | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular Fibrillation | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular Tachycardia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia Alzheimer's Type | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid Artery Stenosis | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid Artery Disease | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain Injury | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebroscclerosis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient Global Amnesia | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory Disturbance | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial Aneurysm | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss Of Consciousness | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic Stroke | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelitis Transverse | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient Ischaemic Attack | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Cupulolithiasis | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract Nuclear | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal Detachment | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Distension | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroesophageal Reflux Disease | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Mucocoele | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric Ulcer Haemorrhage | | | |
| subjects affected / exposed | 3 / 479 (0.63%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric Haemorrhage | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large Intestine Polyp | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal Hernia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal Tubular Necrosis | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Renal Failure Acute | | | |
| subjects affected / exposed | 2 / 479 (0.42%) | 2 / 241 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Osteoarthritis | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Column Stenosis | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compartment Syndrome | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Arthritis Infective | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 3 / 479 (0.63%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis Viral | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Tuberculosis | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative Wound Infection | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Staphylococcal | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis E | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis Chronic | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myringitis Bullous | | | |
| subjects affected / exposed | 0 / 479 (0.00%) | 1 / 241 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 479 (1.46%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scrotal Abscess | | | |
| subjects affected / exposed | 1 / 479 (0.21%) | 0 / 241 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Alirocumab 75/up to 150 mg Q2W | Ezetimibe 10 mg | |
|-------------------------------------------------------|---------------------------------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 77 / 479 (16.08%) | 38 / 241 (15.77%) | |
| Injury, poisoning and procedural complications | | | |
| Accidental Overdose | | | |
| subjects affected / exposed | 30 / 479 (6.26%) | 16 / 241 (6.64%) | |
| occurrences (all) | 44 | 22 | |
| Nervous system disorders | | | |

| | | | |
|----------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| Dizziness subjects affected / exposed occurrences (all) | 21 / 479 (4.38%) 22 | 13 / 241 (5.39%) 15 | |
| Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 31 / 479 (6.47%) 35 | 14 / 241 (5.81%) 15 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 February 2013 | <ul style="list-style-type: none">- Changes in the exclusion criteria related to diabetic control status, history of human immunodeficiency virus, previous participation in any clinical trial of alirocumab or any other anti-PCSK9 monoclonal antibody, laboratory findings during the screening period, and known hypersensitivity to monoclonal antibody.- Change in the reporting of AEs.- Change in the screening period duration and the window for the training visit.- Added the information on a possible contingency strategy in the event the manufacturer faces any performance or supply issues of the auto-injector in order to ensure the continuity of the study treatment without interruption.- Clarification for some safety laboratory parameters.- Clarification was provided regarding the type of cardiovascular (CV) events to be submitted to the Clinical Events Committee (CEC) for adjudication- Added a new section of contraception in the Concomitant medication section.- Precision in the definition of IMP and the way of handling treatment interruption.- Added information on the collection of family medical history to be consistent with what was collected in the e-CRF and with regard to the population enrolled in the study. |
| 26 February 2014 | <ul style="list-style-type: none">- Statistical section was changed.- Addition of the blinding procedures related to pharmacokinetic analysis.- Updated language on cardiovascular events to be reported to the CEC for adjudication and including a clarification on cerebrovascular events.- Added the following sentence "LDL-C was also be measured (via the beta-quantification method) at Week 0 and Week 24".- Updated language on collection of information on partner pregnancy as per other protocol in the ODYSSEY phase 3 program.- Updated language on how to record injection site reactions that were not related to study drug.- Categorization of AEs: updated language on how to record injection site reactions that were not related to study drug. |

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.

Reported results are from first step analysis conducted after all subjects completed 52 Weeks visit.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25687353>