



Clinical trial results:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolemia Who are Intolerant to Statins

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-001221-27 |
| Trial protocol | NO IT GB AT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 18 December 2019 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | R727-CL-1119 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|---------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01709513 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study Name: ODYSSEY ALTERNATIVE |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Regeneron Pharmaceuticals, Inc. |
| Sponsor organisation address | 777 Old Saw Mill River Rd., Tarrytown, United States, 10591 |
| Public contact | Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |
| Scientific contact | Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 19 June 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 May 2014 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

Subjects entered 24 weeks double blind treatment period. The main objective was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab in comparison with ezetimibe 10 mg orally once daily (QD) after 24 weeks in subjects with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [heFH] and non-familial hypercholesterolemia [FH]) who were intolerant to statins.

After completion of double blind treatment period subjects entered open label treatment period wherein all subjects received alirocumab.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

Lipid modifying therapies (LMT): bile acid-binding sequestrants such as cholestyramine, colestipol, and colestesvelam; nicotinic acid; fenofibrate, and omega-3 fatty acids and excluded ezetimibe, statins, red yeast rice, and fibrates other than fenofibrate.

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Norway: 6 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | Israel: 33 |
| Country: Number of subjects enrolled | United States: 214 |
| Worldwide total number of subjects | 314 |
| EEA total number of subjects | 50 |

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) | 170 |
| From 65 to 84 years | 142 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 67 sites in 8 countries. Overall, 519 subjects were screened between 28 September 2012 and 11 Aug 2013, 158 of whom were screen failures. Screen failures were mainly due to exclusion criteria met. After screening, 361 subjects entered into single blind placebo run-in period. 314 subjects were randomized.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction or ischemic stroke. Assignment to treatment arms was done centrally in a 2:2:1 (alirocumab:ezetimibe:atorvastatin) ratio. Endpoints were not reported for statin arm as the purpose of statin arm was only to assess the statin tolerance of population.

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Atorvastatin |

Arm description:

Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT.

| | |
|--|------------------------|
| Arm type | Statin rechallenge arm |
| Investigational medicinal product name | Atorvastatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Atorvastatin over-encapsulated tablets.

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

Dosage and administration details:

Placebo (for alirocumab) administered as a subcutaneous (SC) injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

| | |
|------------------|-----------|
| Arm title | Ezetimibe |
|------------------|-----------|

Arm description:

Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT.

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

| | |
|--|--------------------------------------|
| Dosage and administration details: Ezetimibe over--encapsulated tablet. | |
| Investigational medicinal product name | Placebo (for alirocumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Placebo (for alirocumab) administered as a SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm. | |
| Arm title | Alirocumab 75 mg/up to 150 mg |
| Arm description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk. | |
| Arm type | Experimental |
| Investigational medicinal product name | Alirocumab |
| Investigational medicinal product code | REGN727/SAR236553 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Alirocumab administered as a SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm. | |
| Investigational medicinal product name | Placebo (for atorvastatin/ezetimibe) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: Placebo matched to atorvastatin/ezetimibe over--encapsulated tablet. | |

| Number of subjects in period 1 | Atorvastatin | Ezetimibe | Alirocumab 75 mg/up to 150 mg |
|---------------------------------------|--------------|-----------|-------------------------------|
| Started | 63 | 125 | 126 |
| Treated | 63 | 124 | 126 |
| Completed | 42 | 82 | 96 |
| Not completed | 21 | 43 | 30 |
| Randomized but not treated | - | 1 | - |
| Adverse event | 16 | 31 | 23 |
| Unspecified | 3 | 11 | 7 |
| poor compliance to protocol | 2 | - | - |

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Atorvastatin |
| Reporting group description: Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT. | |
| Reporting group title | Ezetimibe |
| Reporting group description: Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT. | |
| Reporting group title | Alirocumab 75 mg/up to 150 mg |
| Reporting group description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk. | |

| Reporting group values | Atorvastatin | Ezetimibe | Alirocumab 75 mg/up to 150 mg |
|------------------------------------|--------------|-----------|-------------------------------|
| Number of subjects | 63 | 125 | 126 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-----------------|------------------|------------------|
| Age continuous Units: years arithmetic mean standard deviation | 63.4 ± 9.5 | 62.8 ± 10.1 | 64.1 ± 9 |
| Gender categorical Units: Subjects Female Male | 28 35 | 58 67 | 56 70 |
| Low Density Lipoprotein Cholesterol (LDL-C) in mg/dL Calculated LDL-C values were obtained using Friedewald formula. Units: mg/dL arithmetic mean standard deviation | 187.3 ± 59.5 | 193.5 ± 70.9 | 191.1 ± 72.7 |
| LDL-C in mmol/L Calculated LDL-C values were obtained using Friedewald formula. Units: mmol/L arithmetic mean standard deviation | 4.85 ± 1.54 | 5.011 ± 1.837 | 4.951 ± 1.883 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 314 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|--|--|--|
| Age continuous Units: years arithmetic mean | | | |
|---|--|--|--|

| | | | |
|--------------------|---|--|--|
| standard deviation | - | | |
|--------------------|---|--|--|

| | | | |
|---|-----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 142 | | |
| Male | 172 | | |
| Low Density Lipoprotein Cholesterol (LDL-C) in mg/dL | | | |
| Calculated LDL-C values were obtained using Friedewald formula. | | | |
| Units: mg/dL | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| LDL-C in mmol/L | | | |
| Calculated LDL-C values were obtained using Friedewald formula. | | | |
| Units: mmol/L | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Atorvastatin |
| Reporting group description: Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT. | |
| Reporting group title | Ezetimibe |
| Reporting group description: Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT. | |
| Reporting group title | Alirocumab 75 mg/up to 150 mg |
| Reporting group description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk. | |

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 ^[1] |
| End point description: Calculated LDL-C values were obtained from Friedewald formula. Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment. | |
| End point type | Primary |
| End point timeframe: From Baseline to Week 24 | |
| Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant. | |

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|--------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -14.6 (\pm 2.2) | -45 (\pm 2.2) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
| Statistical analysis description: Alirocumab group was compared to the corresponding active control group using an appropriate contrast statement. | |

| | |
|---|---|
| Comparison groups | Alirocumab 75 mg/up to 150 mg v Ezetimibe |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -30.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.6 |
| upper limit | -24.2 |

Notes:

[2] - 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 ^[3] |
|-----------------|--|

End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis) . Modified ITT (mITT) population: all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 123 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -17.1 (± 2) | -52.2 (± 2) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg 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 5% level.

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

| | |
|---|-------------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -35.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.7 |
| upper limit | -29.5 |

Notes:

[4] - 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 ^[5] |
|-----------------|---|

End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment (ITT analysis). ITT population.

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

End point timeframe:

From Baseline to Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -15.6 (± 2) | -47 (± 1.9) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|-------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -31.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.9 |
| upper limit | -26.1 |

Notes:

[6] - 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 ^[7] |
|-----------------|--|

End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 12 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis). mITT population.

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

End point timeframe:

From Baseline to Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 123 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -18 (± 1.8) | -51.2 (± 1.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|-------------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -33.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38 |
| upper limit | -28.2 |

Notes:

[8] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Apolipoprotein (Apo) B at Week 24 - ITT Analysis ^[9] |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 122 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -11.2 (± 1.7) | -36.3 (± 1.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[10] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean difference |
| Point estimate | -25.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.8 |
| upper limit | -20.4 |

Notes:

[10] - 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 ^[11] |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline Apo B value on-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 109 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -14.4 (± 1.4) | -42.6 (± 1.3) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[12] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -28.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.1 |
| upper limit | -24.4 |

Notes:

[12] - 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 ^[13] |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -14.6 (± 1.7) | -40.2 (± 1.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[14] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -25.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.4 |
| upper limit | -20.8 |

Notes:

[14] - 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 ^[15] |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline non-HDL-C value on-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 123 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -17.1 (± 1.5) | -46.9 (± 1.4) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[16] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.9 |
| upper limit | -25.8 |

Notes:

[16] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis ^[17] |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline total-C value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -10.9 (± 1.4) | -31.8 (± 1.4) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[18] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -20.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.7 |
| upper limit | -17 |

Notes:

[18] - 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 ^[19] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|--------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 122 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -11.6 (\pm 1.5) | -36.1 (\pm 1.5) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[20] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -24.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.7 |
| upper limit | -20.4 |

Notes:

[20] - 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 ^[21] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -15.8 (± 1.5) | -41.5 (± 1.5) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[22] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -25.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.9 |
| upper limit | -21.5 |

Notes:

[22] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Total-C at Week 12 - ITT Analysis ^[23] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|--------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -11.6 (\pm 1.2) | -32.7 (\pm 1.2) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[24] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -21.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.5 |
| upper limit | -17.7 |

Notes:

[24] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|--|
| End point title | Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis ^[25] |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to Week 24

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 4.4 | 41.9 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg 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 | Ezetimibe v Alirocumab 75 mg/up to 150 mg |
|-------------------|---|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[26] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 19.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.9 |
| upper limit | 55.2 |

Notes:

[26] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|---|
| End point title | Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis ^[27] |
|-----------------|---|

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first (on-treatment analysis). mITT population.

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

End point timeframe:

Up to Week 24

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 123 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 5.6 | 51.2 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg 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 | Ezetimibe v Alirocumab 75 mg/up to 150 mg |
|-------------------|---|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[28] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 24.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.6 |
| upper limit | 71.9 |

Notes:

[28] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|--|
| End point title | Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT Analysis ^[29] |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to Week 24

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 0.8 | 32.5 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a last observation carried forward (LOCF) approach followed by exact conditional logistic regression model.

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

| | |
|---|--|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[30] |
| Method | Regression, Exact Conditional Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 71.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.1 |
| upper limit | 3022.1 |

Notes:

[30] - Threshold for significance ≤ 0.05 .

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

| | |
|-----------------|---|
| End point title | Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis ^[31] |
|-----------------|---|

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first (on-treatment analysis). mITT population.

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

End point timeframe:

Up to Week 24

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 123 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 0.8 | 39 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a LOCF approach followed by exact conditional logistic regression model.

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

| | |
|---|--|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[32] |
| Method | Regression, Exact Conditional Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 109.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.5 |
| upper limit | 4759.3 |

Notes:

[32] - 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 ^[33] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|----------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -7.3 (\pm 2.5) | -25.9 (\pm 2.4) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg 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 | Ezetimibe v Alirocumab 75 mg/up to 150 mg |
|-------------------|---|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[34] |
| Method | Regression, Robust |
| Parameter estimate | Adjusted Mean Difference |
| Point estimate | -18.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.5 |
| upper limit | -11.8 |

Notes:

[34] - 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 ^[35] |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 24

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 6.8 (± 1.7) | 7.7 (± 1.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Alirocumab 75 mg/up to 150 mg vs Ezetimibe |
|----------------------------|--|

Statistical analysis description:

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

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

| | |
|---|--------------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6997 ^[36] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | 5.6 |

Notes:

[36] - 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 ^[37] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -3.6 (\pm 2.8) | -9.3 (\pm 2.7) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Apo A-1 at Week 24 - ITT Analysis ^[38] |
|-----------------|---|

End point description:

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

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| | | | | |
|-------------------------------------|-----------------|-------------------------------|--|--|
| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 122 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 2.9 (± 1.2) | 4.8 (± 1.2) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis ^[39] |
|-----------------|---|

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 24 regardless of status on- or off-treatment. Lipoprotein (a) ITT population.

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

End point timeframe:

From Baseline to Week 12

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| | | | | |
|----------------------------------|-----------------|-------------------------------|--|--|
| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -4.5 (± 2.3) | -21.7 (± 2.2) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis ^[40] |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 7.6 (± 1.2) | 9 (± 1.2) | | |

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 ^[41] |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 12 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Fasting triglycerides ITT population.

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

End point timeframe:

From Baseline to Week 24

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 | 126 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | -9.4 (± 2.6) | -8 (± 2.5) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis ^[42] |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo A-1 ITT population.

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

End point timeframe:

From Baseline to Week 24

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

| End point values | Ezetimibe | Alirocumab 75 mg/up to 150 mg | | |
|-------------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 122 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 3.9 (± 1) | 5.5 (± 1) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 24

Adverse event reporting additional description:

Treatment emergent adverse events that developed during treatment emergent adverse events period (the time from the first double-blind study treatment [injection or capsules, whichever came first] up to the day of the last double-blind injection + 70 days) are reported.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Atorvastatin |
|-----------------------|--------------|

Reporting group description:

Atorvastatin 20 mg QD for 24 weeks and placebo 'for aliocumab' Q2W for 22 weeks added to stable LMT.

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

Reporting group description:

Alirocumab 75 mg Q2W for 22 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk.

| | |
|-----------------------|-----------|
| Reporting group title | Ezetimibe |
|-----------------------|-----------|

Reporting group description:

Ezetimibe 10 mg QD for 24 weeks and placebo for aliocumab Q2W for 22 weeks added to stable LMT.

| Serious adverse events | Atorvastatin | Alirocumab 75 mg/up to 150 mg | Ezetimibe |
|---|-----------------|-------------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 63 (11.11%) | 12 / 126 (9.52%) | 10 / 124 (8.06%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian epithelial cancer | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic arthritis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 126 (0.00%) | 1 / 124 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|--|---|----------------|-----------------|-----------------|
| Atrial fibrillation | subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 1 / 124 (0.81%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiovascular disorder | subjects affected / exposed | 0 / 63 (0.00%) | 0 / 126 (0.00%) | 1 / 124 (0.81%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve incompetence | subjects affected / exposed | 0 / 63 (0.00%) | 0 / 126 (0.00%) | 1 / 124 (0.81%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | subjects affected / exposed | 1 / 63 (1.59%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | | |
| Loss of consciousness | subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | | |
| Non-Cardiac chest pain | subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 4 / 124 (3.23%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 4 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 126 (0.00%) | 1 / 124 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Peritoneal haemorrhage | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 126 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 126 (0.00%) | 1 / 124 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 126 (0.79%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Atorvastatin | Alirocumab 75 mg/up to 150 mg | Ezetimibe |
|---|------------------|-------------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 63 (55.56%) | 57 / 126 (45.24%) | 63 / 124 (50.81%) |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 4 / 126 (3.17%) | 0 / 124 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 6 / 126 (4.76%) | 6 / 124 (4.84%) |
| occurrences (all) | 4 | 7 | 8 |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------------|-------------------------|-------------------------|
| Fatigue subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 5 | 6 / 126 (4.76%) 6 | 4 / 124 (3.23%) 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia subjects affected / exposed occurrences (all) | 17 / 63 (26.98%) 21 | 31 / 126 (24.60%) 35 | 29 / 124 (23.39%) 35 |
| Muscular weakness subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 1 / 126 (0.79%) 1 | 2 / 124 (1.61%) 2 |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 5 | 7 / 126 (5.56%) 9 | 9 / 124 (7.26%) 10 |
| Muscle spasms subjects affected / exposed occurrences (all) | 7 / 63 (11.11%) 7 | 5 / 126 (3.97%) 7 | 9 / 124 (7.26%) 11 |
| Back pain subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 6 | 5 / 126 (3.97%) 6 | 7 / 124 (5.65%) 9 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 8 / 126 (6.35%) 8 | 10 / 124 (8.06%) 12 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 7 / 126 (5.56%) 7 | 5 / 124 (4.03%) 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 24 January 2013 | The purpose of this amendment was to: - Add an open-label treatment period. - Change the wording of the inclusion/exclusion criteria. - Change the schedule of events. - Make changes to reflect the addition of the open-label extension. |
| 13 February 2013 | The purpose of this amendment was to: - Add contingency language to ensure the continuity of study drug supply without interruption (in the event the manufacturer faced any performance or supply issues of the auto-injector). - Increase some visit windows to allow more scheduling flexibility. - Remove hospitalization for unanticipated coronary revascularization from the list of Clinical Events Committee (CEC) adjudication categories, and add that all coronary revascularizations would be submitted to the CEC. - Make miscellaneous administrative clarifications. |
| 02 May 2013 | The purpose of this amendment was to: - Change vitamin D status requirements. - Clarify allowable retreatment with ezetimibe after discontinuation of study drug. - Make formatting and other corrections. |
| 08 April 2014 | The purpose of this amendment was to: - Modify the primary efficacy analysis population to the ITT population for the primary and secondary efficacy endpoints, which included assessments both on study treatment and off study treatment through the analysis period. - An MMRM was to be used for the primary endpoint and for other continuous secondary endpoints anticipated to have normally distributed data. - For continuous endpoints expected to have non-normally distributed data, the robust regression method was to be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - For binary endpoints, logistic regression method was to be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - Primary and key secondary endpoints was also to be analyzed in the mITT population to assess the drug effect during the study treatment period (on treatment approach). - The lists of key and other secondary efficacy endpoints and estimands (ITT estimand or on-treatment estimand) were adjusted. - Update language on CV events to be reported to the CEC for adjudication, and clarify cerebrovascular events. - Clarify that LDL-C measured and calculated was to be performed at weeks 0 and 24. - Update language on collection of partner pregnancy data, per the ODYSSEY program. - Update categorization of AEs (update language on how to record injection site reactions that were not related to study drug). - Make minor corrections/clarifications. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported