



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Study Followed by an Open Label Treatment Period to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia

Summary

| | |
|--------------------------|--|
| EudraCT number | 2017-001903-60 |
| Trial protocol | SE DK FR IT DE AT Outside EU/EEA NL HU SI ES PL FI BG CZ |
| Global end of trial date | NO 05 August 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 24 June 2023 |
| First version publication date | 22 February 2023 |

| | |
|-------------------------|--|
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Consistency with CTG |
|-------------------------|--|

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC14643 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03510884 |
| WHO universal trial number (UTN) | U1111-1193-0721 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi-aventis Recherche & Développement |
| Sponsor organisation address | 1 Avenue Pierre Brossolette, Chilly-Mazarin, France, 91385 |
| 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001169-PIP01-11 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 August 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 August 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of alirocumab administered every 2 weeks (Q2W) and every 4 weeks (Q4W) versus placebo after 24 weeks of double-blind (DB) treatment on low-density lipoprotein cholesterol (LDL-C) levels in subjects with heterozygous familial hypercholesterolemia (heFH) 8 to 17 years of age on optimal stable daily dose of statin therapy \pm other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 31 May 2018 |
| 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 | Austria: 3 |
| Country: Number of subjects enrolled | Finland: 3 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Poland: 12 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Argentina: 2 |
| Country: Number of subjects enrolled | Brazil: 6 |
| Country: Number of subjects enrolled | Canada: 10 |
| Country: Number of subjects enrolled | Lebanon: 5 |
| Country: Number of subjects enrolled | Mexico: 17 |
| Country: Number of subjects enrolled | South Africa: 1 |
| Country: Number of subjects enrolled | Taiwan: 2 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | United States: 13 |
| Country: Number of subjects enrolled | Czechia: 12 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Country: Number of subjects enrolled | Netherlands: 18 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Russian Federation: 8 |
| Country: Number of subjects enrolled | Slovenia: 2 |
| Country: Number of subjects enrolled | Turkey: 6 |
| Worldwide total number of subjects | 153 |
| EEA total number of subjects | 83 |

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) | 55 |
| Adolescents (12-17 years) | 98 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 43 active sites in 24 countries. A total of 203 subjects were screened between 31-May-2018 and 31-Jul-2020, of whom 50 were screen failures. Screen failures were mainly due to exclusion criteria met. A total of 153 subjects were randomised with a 2:1 ratio to receive study treatment (alirocumab: placebo).

Pre-assignment

Screening details:

Randomisation was stratified according to previous participation (yes or no) in the Phase 2 DFI14223 (EudraCT number: 2015-003766-85) study and Baseline body weight (BW) (less than [$<$] 50 kilograms (kg) or greater than or equal to [\geq] 50 kg).

Period 1

| | |
|------------------------------|-------------------------------------|
| Period 1 title | Double-blind Period (up to Week 24) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer |

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | DB Period: Placebo Q2W |

Arm description:

Subjects received subcutaneous (SC) injection of placebo (matched to alicumab) based on their BW (<50 kg or ≥ 50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT.

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

Dosage and administration details:

Placebo (matched to alicumab) SC injection based on BW (<50 kg or ≥ 50 kg) Q2W for 24 weeks with stable LMT.

| | |
|------------------|---------------------------|
| Arm title | DB Period: Alirocumab Q2W |
|------------------|---------------------------|

Arm description:

Subjects received SC injection of alicumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥ 50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥ 110 milligrams per decilitre (mg/dL) (2.85 millimoles per litre [mmol/L]) at Week 8.

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

Dosage and administration details:

Alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥ 50 kg) SC injection Q2W for 24 weeks with stable LMT. Up-titrated dose: 75 mg or 150 mg Q2W from Week 12, when LDL-C level was ≥ 110 mg/dL (2.85 mmol/L) at Week 8.

| | |
|------------------|------------------------|
| Arm title | DB Period: Placebo Q4W |
|------------------|------------------------|

Arm description:

Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT.

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

Dosage and administration details:

Placebo (matched to alirocumab) SC injection based on BW (<50 kg or ≥50 kg) Q4W for 24 weeks with stable LMT.

| | |
|------------------|---------------------------|
| Arm title | DB Period: Alirocumab Q4W |
|------------------|---------------------------|

Arm description:

Subjects received SC injection of alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8.

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

Dosage and administration details:

Alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) SC injection Q4W for 24 weeks with stable LMT. Up-titrated dose: 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8.

| Number of subjects in period 1 | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W |
|--|------------------------|---------------------------|------------------------|
| Started | 25 | 49 | 27 |
| Completed | 25 | 45 | 26 |
| Not completed | 0 | 4 | 1 |
| Noncompliance to investigational medicinal product | - | 2 | - |
| Other - Unspecified | - | - | 1 |
| Adverse event | - | - | - |
| Subject moved | - | 1 | - |
| Life events made continuing too difficult | - | 1 | - |

| Number of subjects in period 1 | DB Period: Alirocumab Q4W |
|--|---------------------------|
| Started | 52 |
| Completed | 49 |
| Not completed | 3 |
| Noncompliance to investigational medicinal product | - |
| Other - Unspecified | 1 |
| Adverse event | 2 |

| | |
|---|---|
| Subject moved | - |
| Life events made continuing too difficult | - |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Open Label (OL) Period (up to Week 104) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | OL Period: Placebo/Alirocumab Q2W |

Arm description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

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

Dosage and administration details:

Alirocumab 40 milligrams (mg) (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject low density lipoprotein cholesterol (LDL-C) value, alirocumab dose was either uptitrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|------------------|---------------------------|
| Arm title | OL Period: Alirocumab Q2W |
|------------------|---------------------------|

Arm description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

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

Dosage and administration details:

Alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|------------------|-----------------------------------|
| Arm title | OL Period: Placebo/Alirocumab Q4W |
|------------------|-----------------------------------|

Arm description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

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

Dosage and administration details:

Alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

| | |
|------------------|---------------------------|
| Arm title | OL Period: Alirocumab Q4W |
|------------------|---------------------------|

Arm description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

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

Dosage and administration details:

Alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

| Number of subjects in period 2 | OL Period: Placebo/Alirocumab Q2W | OL Period: Alirocumab Q2W | OL Period: Placebo/Alirocumab Q4W |
|---|---|------------------------------|---|
| | | | |
| Started | 25 | 46 | 25 |
| Completed | 22 | 43 | 24 |
| Not completed | 3 | 3 | 1 |
| Other - Unspecified | 1 | 1 | - |
| Adverse event | 1 | - | - |
| Subject moved | 1 | - | 1 |
| Life events made continuing too difficult | - | 1 | - |
| Lack of efficacy | - | 1 | - |

| Number of subjects in period 2 | OL Period: Alirocumab Q4W |
|---|------------------------------|
| Started | 49 |
| Completed | 49 |
| Not completed | 0 |
| Other - Unspecified | - |
| Adverse event | - |
| Subject moved | - |
| Life events made continuing too difficult | - |
| Lack of efficacy | - |

Baseline characteristics

Reporting groups

| | |
|--|---------------------------|
| Reporting group title | DB Period: Placebo Q2W |
| Reporting group description: | |
| Subjects received subcutaneous (SC) injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. | |
| Reporting group title | DB Period: Alirocumab Q2W |
| Reporting group description: | |
| Subjects received SC injection of alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 milligrams per decilitre (mg/dL) (2.85 millimoles per litre [mmol/L]) at Week 8. | |
| Reporting group title | DB Period: Placebo Q4W |
| Reporting group description: | |
| Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. | |
| Reporting group title | DB Period: Alirocumab Q4W |
| Reporting group description: | |
| Subjects received SC injection of alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8. | |

| Reporting group values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W |
|---|------------------------|---------------------------|------------------------|
| Number of subjects | 25 | 49 | 27 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 13.2 | 12.5 | 12.8 |
| standard deviation | ± 2.4 | ± 2.7 | ± 3.0 |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 30 | 15 |
| Male | 17 | 19 | 12 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 4 |
| Asian | 1 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 23 | 42 | 22 |
| More than one race | 1 | 4 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Low-Density Lipoprotein Cholesterol | | | |
| Calculated LDL-C values were obtained using Friedewald formula: LDL-C = Total cholesterol - High-density lipoprotein cholesterol [HDL-C] - [Triglyceride/5] | | | |
| Units: mg/dL | | | |
| arithmetic mean | 175.29 | 169.69 | 176.57 |

| | | | |
|--------------------|---------|---------|---------|
| standard deviation | ± 50.23 | ± 46.74 | ± 49.01 |
|--------------------|---------|---------|---------|

| Reporting group values | DB Period: Alirocumab Q4W | Total | |
|------------------------------------|------------------------------|-------|--|
| Number of subjects | 52 | 153 | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-------------------|-----|--|
| Age continuous Units: years arithmetic mean standard deviation | 13.1 ± 3.0 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 34 | 87 | |
| Male | 18 | 66 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 12 | 16 | |
| Asian | 0 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | |
| Black or African American | 1 | 3 | |
| White | 38 | 125 | |
| More than one race | 0 | 5 | |
| Unknown or Not Reported | 1 | 1 | |
| Low-Density Lipoprotein Cholesterol | | | |
| Calculated LDL-C values were obtained using Friedewald formula: LDL-C = Total cholesterol - High-density lipoprotein cholesterol [HDL-C] - [Triglyceride/5]) | | | |
| Units: mg/dL arithmetic mean standard deviation | 176.79 ± 53.93 | - | |

End points

End points reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | DB Period: Placebo Q2W |
| Reporting group description: Subjects received subcutaneous (SC) injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. | |
| Reporting group title | DB Period: Alirocumab Q2W |
| Reporting group description: Subjects received SC injection of alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 milligrams per decilitre (mg/dL) (2.85 millimoles per litre [mmol/L]) at Week 8. | |
| Reporting group title | DB Period: Placebo Q4W |
| Reporting group description: Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. | |
| Reporting group title | DB Period: Alirocumab Q4W |
| Reporting group description: Subjects received SC injection of alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8. | |
| Reporting group title | OL Period: Placebo/Alirocumab Q2W |
| Reporting group description: After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg). | |
| Reporting group title | OL Period: Alirocumab Q2W |
| Reporting group description: After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg). | |
| Reporting group title | OL Period: Placebo/Alirocumab Q4W |
| Reporting group description: After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg). | |
| Reporting group title | OL Period: Alirocumab Q4W |
| Reporting group description: After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg). | |

| | |
|----------------------------|------------------------|
| Subject analysis set title | Placebo/Alirocumab Q2W |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|----------------------------|-----------------|
| Subject analysis set title | Alirocumab Q2W |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects received SC injection of alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level was ≥110 mg/dL (2.85 mmol/L) at Week 8. After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|----------------------------|------------------------|
| Subject analysis set title | Placebo/Alirocumab Q4W |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

| | |
|----------------------------|-----------------|
| Subject analysis set title | Alirocumab Q4W |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects received SC injection of alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W for 24 weeks in DB treatment period added to stable LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8. After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

Primary: DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 24: Intent-to-treat (ITT) Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 24: Intent-to-treat (ITT) Estimand |
|-----------------|---|

End point description:

Adjusted least square (LS) means and standard errors (SE) were obtained from mixed-effect model with repeated measures (MMRM) model. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population which included all randomised subjects who were analysed according to the treatment group allocated by randomisation. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 9.7 (± 4.3) | -33.6 (± 3.4) | -4.4 (± 3.7) | -38.2 (± 4.0) |

Statistical analyses

| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|--|--|
| Statistical analysis description: | |
| The MMRM model included fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DF114223 study, Baseline BW [<50 or >=50 kg]) as per interactive voice response system (IVRS), time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline LDL-C value and Baseline value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 ^[2] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -43.3 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -56 |
| upper limit | -30.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.5 |

Notes:

[1] - Bonferroni adjustment was applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its placebo group for the primary efficacy endpoint.

[2] - The threshold for statistical significance was 0.025 level.

| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|---|--|
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline LDL-C value and Baseline value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.0001 ^[4] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -33.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -46.4 |
| upper limit | -21.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.5 |

Notes:

[3] - Bonferroni adjustment was applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its placebo group for the primary efficacy endpoint.

[4] - The threshold for statistical significance was 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 12: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Week 12: ITT Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 10.7 (± 3.6) | -34.8 (± 3.0) | 2.3 (± 3.6) | -39.2 (± 3.3) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|----------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline LDLC value and Baseline value by time-point interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.0001 ^[6] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -45.5 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -56.3 |
| upper limit | -34.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.7 |

Notes:

[5] - Hierarchical testing method was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints were reported and independently for each dosing regimen. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level. Statistical significance of the primary endpoint was required before testing the first secondary endpoint for each dosing regimen independently.

[6] - Threshold for significance at 0.025 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-----------------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or ≥50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline LDL-C value and Baseline value by time-point interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | < 0.0001 ^[8] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -41.5 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -52.7 |
| upper limit | -30.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.9 |

Notes:

[7] - A hierarchical testing method 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 and independently for each dosing regimen. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level. Statistical significance of the primary endpoint was required before testing the first secondary endpoint for each dosing regimen independently.

[8] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein B (Apo B) at Week 24: ITT Estimand

| | |
|---|--|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein B (Apo B) at Week 24: ITT Estimand |
| End point description: | |
| Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | 10.4 (± 2.8) | -27.4 (± 3.2) | -3.6 (± 3.9) | -34.3 (± 2.9) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Apo B value and Baseline Apo B value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | < 0.0001 ^[10] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -37.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -47.5 |
| upper limit | -28.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.2 |

Notes:

[9] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[10] - Threshold for significance at 0.025 level.

| | |
|----------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|----------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or ≥ 50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Apo B value and Baseline Apo B value by timepoint interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | < 0.0001 ^[12] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -30.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -42 |
| upper limit | -19.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.9 |

Notes:

[11] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[12] - Threshold for significance at 0.025 level.

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

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 9.7 (\pm 3.9) | -31.0 (\pm 3.2) | -3.7 (\pm 4.0) | -35.6 (\pm 3.5) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline non-HDL-C value and Baseline non-HDL-C value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | < 0.0001 ^[14] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -40.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -52.2 |
| upper limit | -29.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5 |

Notes:

[13] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[14] - Threshold for significance at 0.025 level.

| | |
|---|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline non-HDL-C value and Baseline non-HDL-C value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | < 0.0001 ^[16] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -31.9 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -44.1 |
| upper limit | -19.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.3 |

Notes:

[15] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[16] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Total Cholesterol (Total-C)

at Week 24: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24: ITT Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 7.4 (± 3.0) | -23.4 (± 2.5) | -4.4 (± 3.3) | -27.7 (± 2.9) |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|-----------------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DF114223 study, Baseline BW [<50 or ≥ 50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Total-C value and Baseline Total-C value by time-point interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | < 0.0001 ^[18] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -30.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -39.8 |
| upper limit | -21.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.9 |

Notes:

[17] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[18] - Threshold for significance at 0.025 level.

| | |
|---|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Statistical analysis description: The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or ≥ 50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Total-C value and Baseline Total-C value by timepoint interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | < 0.0001 ^[20] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -23.3 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -33.5 |
| upper limit | -13.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.4 |

Notes:

[19] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[20] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein B at Week 12: ITT Estimand

| | |
|---|--|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein B at Week 12: ITT Estimand |
| End point description: Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 12 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | 8.9 (\pm 3.1) | -30.0 (\pm 2.5) | 1.1 (\pm 3.2) | -31.7 (\pm 2.9) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DF114223 study, Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Apo B value and Baseline Apo B value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[21] |
| P-value | < 0.0001 ^[22] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -38.9 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -48.2 |
| upper limit | -29.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4 |

Notes:

[21] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[22] - Threshold for significance at 0.025 level.

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Apo B value and Baseline Apo B value by timepoint interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | < 0.0001 ^[24] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -32.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -42.8 |
| upper limit | -22.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.3 |

Notes:

[23] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

Secondary: DB Period: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol at Week 12: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol at Week 12: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 9.8 (± 3.8) | -33.0 (± 2.8) | 2.8 (± 3.5) | -34.7 (± 2.9) |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|-----------------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥ 50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Non-HDL-C value and Baseline Non-HDL-C value by time-point interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[25] |
| P-value | < 0.0001 ^[26] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -42.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -53.8 |
| upper limit | -31.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.7 |

Notes:

[25] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[26] - Threshold for significance at 0.025 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-----------------------------------|--|

Statistical analysis description:

The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or ≥ 50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline non-HDL-C value and Baseline non-HDL-C value by time-point interaction. Comparison was performed using an appropriate contrast.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[27] |
| P-value | < 0.0001 ^[28] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -37.5 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -47.9 |
| upper limit | -27 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.5 |

Notes:

[27] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[28] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Total Cholesterol at Week 12: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Total Cholesterol at Week 12: ITT Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model including all available post-baseline data. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | 7.5 (\pm 2.9) | -25.3 (\pm 2.2) | 0.9 (\pm 2.5) | -27.0 (\pm 2.3) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Total-C value and Baseline Total-C value by time-point interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[29] |
| P-value | < 0.0001 ^[30] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -32.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -41.3 |
| upper limit | -24.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.7 |

Notes:

[29] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[30] - Threshold for significance at 0.025 level.

| | |
|--|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Statistical analysis description: | |
| The MMRM model included the fixed categorical effects of treatment group (alirocumab, placebo), randomisation strata (Baseline BW [<50 or >=50 kg]) as per IVRS, time point, treatment-by-time point interaction, and BW strata-by-time point interaction, as well as the continuous fixed covariates of Baseline Total-C value and Baseline Total-C value by timepoint interaction. Comparison was performed using an appropriate contrast. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[31] |
| P-value | < 0.0001 ^[32] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -27.9 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -35.6 |
| upper limit | -20.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.4 |

Notes:

[31] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[32] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol Level Lower Than (<) 130 mg/dL (3.37 mmol/L) at Week 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol Level Lower Than (<) 130 mg/dL (3.37 mmol/L) at Week 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Week 24 were obtained from multiple imputation approach for handling of missing data. All available post-baseline data up to Week 24 were included in the imputation model. Analysis was performed on ITT population.

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

End point timeframe:

At Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 8.0 | 73.3 | 22.2 | 76.3 |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|----------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥50 kg]) as per IVRS included the fixed categorical effect of treatment group and continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of different imputed data sets, using Rubin's formulae.

| | |
|-------------------|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[33] |
| P-value | = 0.0001 ^[34] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 77.6 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 6.3 |
| upper limit | 960 |

Notes:

[33] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[34] - Threshold for significance at 0.025 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-----------------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (Baseline BW [<50 or ≥50 kg]) as per IVRS included the fixed categorical effect of treatment group and the continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[35] |
| P-value | < 0.0001 ^[36] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 14.9 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 3.2 |
| upper limit | 69.8 |

Notes:

[35] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[36] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol Level <130 mg/dL (3.37 mmol/L) at Week 12: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol Level <130 mg/dL (3.37 mmol/L) at Week 12: ITT Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Week 12 were obtained from multiple imputation approach for handling of missing data. All available post-baseline data up to Week 12 were included in the imputation model. Analysis was performed on ITT population.

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

End point timeframe:

At Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 16.4 | 70.6 | 12.9 | 72.6 |

Statistical analyses

| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|--|--|
| Statistical analysis description: | |
| Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥ 50 kg]) as per IVRS included the fixed categorical effect of treatment group and continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[37] |
| P-value | < 0.0001 ^[38] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 26.5 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 4 |
| upper limit | 174.8 |

Notes:

[37] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[38] - Threshold for significance at 0.025 level.

| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|--|--|
| Statistical analysis description: | |
| Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (Baseline BW [<50 or ≥ 50 kg]) as per IVRS included the fixed categorical effect of treatment group and the continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[39] |
| P-value | < 0.0001 ^[40] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 40.9 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 5.7 |
| upper limit | 290.9 |

Notes:

[39] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[40] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percentage of Subjects Achieving Low Density Lipoprotein Cholesterol <110 mg/dL (2.84 mmol/L) at Week 24: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percentage of Subjects Achieving Low Density Lipoprotein Cholesterol <110 mg/dL (2.84 mmol/L) at Week 24: ITT Estimand |
|-----------------|---|

End point description:

Adjusted percentages at Week 24 were obtained from multiple imputation approach for handling of missing data. All available post-baseline data up to Week 24 were included in the imputation model. Analysis was performed on ITT population.

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

End point timeframe:

At Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 4.0 | 57.2 | 9.0 | 67.2 |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|----------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥50 kg]) as per IVRS included the fixed categorical effect of treatment group and the continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of different imputed data sets, using Rubin's formulae.

| | |
|-------------------|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[41] |
| P-value | = 0.0011 ^[42] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 52.7 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 3.5 |
| upper limit | 804.3 |

Notes:

[41] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[42] - Threshold for significance at 0.025 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-----------------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (Baseline BW [<50 or ≥ 50 kg]) as per IVRS included the fixed categorical effect of treatment group and the continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[43] |
| P-value | = 0.0006 ^[44] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 43.1 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 3.7 |
| upper limit | 498.6 |

Notes:

[43] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[44] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percentage of Subjects Achieving Low Density Lipoprotein Cholesterol <110 mg/dL (2.84 mmol/L) at Week 12: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percentage of Subjects Achieving Low Density Lipoprotein Cholesterol <110 mg/dL (2.84 mmol/L) at Week 12: ITT Estimand |
|-----------------|---|

End point description:

Adjusted percentages at Week 12 were obtained from multiple imputation approach for handling of missing data for Q4W. All available post-baseline data up to Week 12 were included in the imputation model. For Q2W, adjusted percentages at Week 12 were obtained from last observation carried forward approach (LOCF) to handle missing on-treatment LDL-C values as well as missing post-treatment LDL-C values in subjects who discontinued treatment due to the coronavirus disease-2019 pandemic. Other post-treatment missing values were considered as failure. Analysis was performed on ITT population.

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

End point timeframe:

At Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 0.0 | 61.2 | 4.3 | 57.0 |

Statistical analyses

| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|---|--|
| Statistical analysis description: The LOCF approach followed by exact conditional logistic regression model. The exact conditional logistic regression model stratified by randomisation factors (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or >=50 kg]) as per IVRS included the fixed categorical effect of treatment group and the quartiles of the Baseline LDL-C value. Odds ratios and confidence intervals estimated from exact conditional logistic regression model. | |
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[45] |
| P-value | < 0.0001 ^[46] |
| Method | Exact conditional logistic regression |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 41.3 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 6.6 |
| upper limit | 99999 |

Notes:

[45] - Testing according to hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen). Here, 99999, a space filler = percentage of subjects reaching LDL-C level lower than 110 mg/dL was 0% in placebo arm, as a result it was possible to derive estimated odds-ratio, but estimated confidence interval (CI) was very wide, with upper limit estimated to infinity, therefore upper limit of 97.5% CI was not available to report.

[46] - Threshold for significance at 0.025 level.

| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|---|--|
| Statistical analysis description: Multiple imputation approach followed by logistic regression model, stratified by randomisation factors (Baseline BW [<50 or >=50 kg]) as per IVRS included the fixed categorical effect of treatment group and the continuous fixed covariate of Baseline LDL-C value. Combined estimate for odds ratio was obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formulae. | |
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[47] |
| P-value | = 0.0005 ^[48] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 104.8 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 5.2 |
| upper limit | 2095.9 |

Notes:

[47] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[48] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Lipoprotein (a) at Week 24: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Lipoprotein (a) at Week 24: ITT Estimand |
|-----------------|---|

End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data up to Week 24. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on ITT population.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 0.5 (± 5.3) | -14.7 (± 4.1) | 2.5 (± 7.1) | -22.4 (± 5.0) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|----------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by robust regression model, included the fixed categorical effect of treatment group and randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥50 kg]) as per IVRS and the continuous fixed covariate of Baseline lipoprotein (a) value.

| | |
|-------------------|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[49] |
| P-value | = 0.0237 ^[50] |
| Method | Robust regression model |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -15.2 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -30.3 |
| upper limit | -0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.7 |

Notes:

[49] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[50] - Threshold for significance at 0.025 level.

| | |
|-----------------------------------|--|
| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-----------------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by robust regression model. The robust regression model included the fixed categorical effect of treatment group and randomisation strata (Baseline BW [<50 or ≥ 50 kg]) as per IVRS and the continuous fixed covariate of Baseline lipoprotein (a) value.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[51] |
| P-value | = 0.0043 ^[52] |
| Method | Robust regression model |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -24.9 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -44.4 |
| upper limit | -5.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.7 |

Notes:

[51] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[52] - Threshold for significance at 0.025 level.

Secondary: DB Period: Percent Change From Baseline in Lipoprotein (a) at Week 12: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Lipoprotein (a) at Week 12: ITT Estimand |
|-----------------|---|

End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data up to Week 12. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on ITT population.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | -7.1 (\pm 5.9) | -12.7 (\pm 3.9) | -2.5 (\pm 6.9) | -16.0 (\pm 5.1) |

Statistical analyses

| Statistical analysis title | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by robust regression model. The robust regression model included the fixed categorical effect of treatment group and randomisation strata (previous participation [yes or no] to DFI14223 study, Baseline BW [<50 or ≥ 50 kg]) as per IVRS and the continuous fixed covariate of Baseline lipoprotein (a) value.

| | |
|---|--|
| Comparison groups | DB Period: Placebo Q2W v DB Period: Alirocumab Q2W |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[53] |
| P-value | = 0.4288 ^[54] |
| Method | Robust regression model |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -5.6 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -21.7 |
| upper limit | 10.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.1 |

Notes:

[53] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[54] - Threshold for significance at 0.025 level.

| Statistical analysis title | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Multiple imputation approach followed by robust regression model. The robust regression model included the fixed categorical effect of treatment group and randomisation strata (Baseline BW [<50 or ≥ 50 kg]) as per IVRS and the continuous fixed covariate of Baseline lipoprotein (a) value.

| | |
|-------------------|--|
| Comparison groups | DB Period: Placebo Q4W v DB Period: Alirocumab Q4W |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[55] |
| P-value | = 0.1148 ^[56] |
| Method | Robust regression model |
| Parameter estimate | Adjusted mean difference |
| Point estimate | -13.5 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -32.7 |
| upper limit | 5.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.6 |

Notes:

[55] - Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant for the considered dosing regimen).

[56] - Threshold for significance at 0.025 level.

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

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | -0.8 (± 2.1) | 5.6 (± 1.4) | -1.1 (± 2.7) | 3.4 (± 2.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Fasting Triglycerides (TG) at Week 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Fasting Triglycerides (TG) at Week 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data up to Week 24. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on ITT population.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 7.7 (± 8.4) | 11.9 (± 6.3) | 12.2 (± 8.2) | -6.8 (± 5.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein A1 (Apo A1) at Week 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein A1 (Apo A1) at Week 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | -0.1 (± 2.6) | 1.0 (± 1.5) | -4.5 (± 2.6) | 4.4 (± 2.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in High-Density Lipoprotein Cholesterol at Week 12: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in High-Density Lipoprotein Cholesterol at Week 12: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | -2.2 (± 3.2) | 3.5 (± 2.0) | -3.5 (± 3.2) | 4.0 (± 2.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Fasting Triglycerides (TG) at Week 12: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Fasting Triglycerides (TG) at Week 12: ITT Estimand |
|-----------------|--|

End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data up to Week 12. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on ITT population.

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

End point timeframe:

Baseline, Week 12

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 6.5 (± 7.4) | -2.2 (± 5.0) | 7.8 (± 8.4) | -0.3 (± 6.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein A1 at Week 12: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein A1 at Week 12: ITT Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 12 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | -0.1 (± 1.8) | -1.7 (± 1.7) | -0.7 (± 3.1) | 5.0 (± 1.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Weeks 12, and 24: On-treatment Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Low Density Lipoprotein Cholesterol at Weeks 12, and 24: On-treatment Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st investigational medicinal product (IMP) injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W

regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on modified intent-to-treat (mITT) population which included all randomised subjects who took at least one dose or part of a dose of the IMP injection. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12, and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 10.7 (± 3.6) | -34.8 (± 3.0) | 2.3 (± 3.6) | -39.2 (± 3.3) |
| Week 24 | 9.7 (± 4.3) | -33.6 (± 3.4) | -4.4 (± 3.7) | -38.2 (± 4.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein B at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein B at Weeks 12 and 24: On-treatment Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 8.9 (± 3.1) | -30.0 (± 2.5) | 1.1 (± 3.2) | -31.7 (± 2.9) |
| Week 24 | 10.4 (± 2.8) | -27.4 (± 3.2) | -3.6 (± 3.9) | -34.3 (± 2.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol at Weeks 12 and 24: On-treatment Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 9.8 (± 3.8) | -33.0 (± 2.8) | 2.8 (± 3.5) | -34.7 (± 2.9) |
| Week 24 | 9.7 (± 3.9) | -31.0 (± 3.2) | -3.7 (± 4.0) | -35.6 (± 3.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Total Cholesterol at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Total Cholesterol at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP

injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 7.5 (± 2.9) | -25.3 (± 2.2) | 0.9 (± 2.5) | -27.0 (± 2.3) |
| Week 24 | 7.4 (± 3.0) | -23.4 (± 2.5) | -4.4 (± 3.3) | -27.7 (± 2.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol < 130 mg/dL (3.37 mmol/L) at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol < 130 mg/dL (3.37 mmol/L) at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for those who stopped IMP before switch to Q2W regimen, + 21 days otherwise. Analysis was performed on mITT population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 16.4 | 70.6 | 12.9 | 72.6 |

| | | | | |
|---------|-----|------|------|------|
| Week 24 | 8.0 | 73.3 | 22.2 | 76.3 |
|---------|-----|------|------|------|

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol < 110 mg/dL (2.84 mmol/L) at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved Low Density Lipoprotein Cholesterol < 110 mg/dL (2.84 mmol/L) at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for those who stopped IMP before switch to Q2W regimen, + 21 days otherwise. Analysis was performed on mITT population.

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

End point timeframe:

Weeks 12 and 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 0.1 | 61.7 | 4.3 | 57.0 |
| Week 24 | 4.0 | 57.2 | 9.0 | 67.2 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Lipoprotein (a) at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Lipoprotein (a) at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline on-treatment data up to Week 12 and Week 24, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for those who stopped IMP before switch

to Q2W regimen, + 21 days otherwise. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on mITT population.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | | | | |
| Week 12 | -7.099 (± 5.923) | -12.746 (± 3.889) | -2.545 (± 6.851) | -16.042 (± 5.139) |
| Week 24 | 0.492 (± 5.254) | -14.748 (± 4.083) | 2.468 (± 7.135) | -22.418 (± 5.030) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Apolipoprotein A1 at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change From Baseline in Apolipoprotein A1 at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-Baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | -0.1 (± 1.8) | -1.7 (± 1.7) | -0.7 (± 3.1) | 5.0 (± 1.7) |
| Week 24 | -0.1 (± 2.6) | 1.0 (± 1.5) | -4.5 (± 2.6) | 4.4 (± 2.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 12 and 24: On-treatment Estimand

| | |
|--|---|
| End point title | DB Period: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 12 and 24: On-treatment Estimand |
| End point description: Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 day otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint. | |
| End point type | Secondary |
| End point timeframe: Baseline, Weeks 12, and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | -2.2 (± 3.2) | 3.5 (± 2.0) | -3.5 (± 3.2) | 4.0 (± 2.2) |
| Week 24 | -0.8 (± 2.1) | 5.6 (± 1.4) | -1.1 (± 2.7) | 3.4 (± 2.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change From Baseline in Fasting Triglycerides at Weeks 12 and 24: On-treatment Estimand

| | |
|---|--|
| End point title | DB Period: Percent Change From Baseline in Fasting Triglycerides at Weeks 12 and 24: On-treatment Estimand |
| End point description: Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline on-treatment data up to Week 12 and Week 24, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for those who stopped IMP before switch | |

to Q2W regimen, + 21 days otherwise. Combined estimates and SE were obtained by combining adjusted means and SE from robust regression model analyses of the different imputed data sets. Analysis was performed on mITT population.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12, and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|----------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percent change | | | | |
| arithmetic mean (standard error) | | | | |
| Week 12 | 6.5 (± 7.4) | -2.2 (± 5.0) | 7.8 (± 8.4) | -0.3 (± 6.0) |
| Week 24 | 7.7 (± 8.4) | 11.9 (± 6.3) | 12.2 (± 8.2) | -6.8 (± 5.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 12 and 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 12 and 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 12 and Week 24 were used and missing data were accounted for by the MMRM model. MMRM model was run on subjects with a Baseline value and a post-baseline value for at least one timepoint used in the model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 12, and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: ratio (Apo B/Apo A-1) | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 0.1 (± 0.0) | -0.2 (± 0.0) | 0.0 (± 0.0) | -0.3 (± 0.0) |
| Week 24 | 0.1 (± 0.0) | -0.2 (± 0.0) | 0.0 (± 0.0) | -0.3 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|---|
| End point title | DB Period: Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 12 and 24: On-treatment Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. MMRM model was run on subjects with a Baseline value and at one on-treatment post-baseline value for a timepoint used in the model. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Weeks 12, and 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 47 | 26 | 49 |
| Units: ratio (Apo B/Apo A-1) | | | | |
| least squares mean (standard error) | | | | |
| Week 12 | 0.1 (± 0.0) | -0.2 (± 0.0) | 0.0 (± 0.0) | -0.3 (± 0.0) |
| Week 24 | 0.1 (± 0.0) | -0.2 (± 0.0) | 0.0 (± 0.0) | -0.3 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Who Achieved at Least 30 Percent (%) Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved at Least 30 Percent (%) Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model. Analysis was performed on

ITT population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 0.8 | 65.8 | 4.2 | 70.8 |
| Week 24 | 4.0 | 66.7 | 18.5 | 72.5 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Achieved at Least 30% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Achieved at Least 30% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for those who stopped IMP before switch to Q2W regimen, + 21 days otherwise. Analysis was performed on mITT population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 0.8 | 65.8 | 4.2 | 70.8 |
| Week 24 | 4.0 | 66.7 | 18.5 | 72.5 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Who Achieved at Least 50% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: ITT Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percentage of Subjects Who Achieved at Least 50% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: ITT Estimand |
|-----------------|---|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model. Analysis was performed on ITT population.

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

End point timeframe:

At Weeks 12 and 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 0.0 | 25.2 | 0.1 | 31.9 |
| Week 24 | 0.0 | 21.6 | 9.1 | 32.4 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects Who Achieved at Least 50% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: On-treatment Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percentage of Subjects Who Achieved at Least 50% Reduction in Low Density Lipoprotein Cholesterol Level From Baseline at Weeks 12 and 24: On-treatment Estimand |
|-----------------|--|

End point description:

Adjusted percentages at Weeks 12 and 24 were obtained from multiple imputation approach for handling of missing data followed by logistic regression model. All available post-baseline on-treatment data up to Week 12 and Week 24 were included in the imputation model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP

injection + 35 days for those who stopped IMP before switch to Q2W regimen, + 21 days otherwise. Analysis was performed on mITT population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Weeks 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 | 0.0 | 25.2 | 0.1 | 31.9 |
| Week 24 | 0.0 | 21.6 | 9.1 | 32.4 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Weeks 8, 12 and 24: ITT Estimand

| | |
|-----------------|--|
| End point title | DB Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Weeks 8, 12 and 24: ITT Estimand |
|-----------------|--|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline data available up to Week 8, Week 12 and Week 24 were used and missing data were accounted for by the MMRM model. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Weeks 8, 12 and 24 | |

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 8 | 7.1 (± 4.2) | -35.4 (± 3.6) | -3.8 (± 3.5) | -42.0 (± 2.8) |
| Week 12 | 10.7 (± 3.6) | -34.8 (± 3.0) | 2.3 (± 3.6) | -39.2 (± 3.3) |
| Week 24 | 9.7 (± 4.3) | -33.6 (± 3.4) | -4.4 (± 3.7) | -38.2 (± 4.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Weeks 8, 12 and 24: On-treatment Estimand

| | |
|-----------------|---|
| End point title | DB Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Weeks 8, 12 and 24: On-treatment Estimand |
|-----------------|---|

End point description:

Adjusted LS means and SE were obtained from MMRM model. All post-baseline on-treatment data available up to Week 8, Week 12 and Week 24 were used for the MMRM model, i.e., for Q2W data: from 1st IMP injection up to last IMP injection + 21 days and for Q4W data: from 1st IMP injection up to last IMP injection + 35 days for who stopped IMP before switch to Q2W regimen, + 21 days otherwise. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline to Weeks 8, 12 and 24

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|-------------------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 49 | 26 | 50 |
| Units: percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 8 | 7.1 (± 4.2) | -35.4 (± 3.6) | -3.8 (± 3.5) | -42.0 (± 2.8) |
| Week 12 | 10.7 (± 3.6) | -34.8 (± 3.0) | 2.3 (± 3.6) | -39.2 (± 3.3) |
| Week 24 | 9.7 (± 4.3) | -33.6 (± 3.4) | -4.4 (± 3.7) | -38.2 (± 4.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Week 104: ITT Estimand

| | |
|-----------------|--|
| End point title | OL Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Week 104: ITT Estimand |
|-----------------|--|

End point description:

Percent Change in LDL-C from Baseline to Week 104 was reported in this endpoint. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with available data for this endpoint. The ITT estimand was analysed by considering all the post-baseline (including both on- and post-treatment) LDL-C values for the analysis.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 104 | |

| End point values | OL Period: Placebo/Alirocu mab Q2W | OL Period: Alirocumab Q2W | OL Period: Placebo/Alirocu mab Q4W | OL Period: Alirocumab Q4W |
|-------------------------------------|--|---------------------------------|--|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 45 | 23 | 47 |
| Units: percent change | | | | |
| least squares mean (standard error) | -23.3 (± 4.9) | -22.2 (± 5.6) | -27.1 (± 7.0) | -23.7 (± 4.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: OL Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Week 104: On-treatment Estimand

| | |
|-----------------|---|
| End point title | OL Period: Percent Change in Low Density Lipoprotein Cholesterol From Baseline to Week 104: On-treatment Estimand |
|-----------------|---|

End point description:

Percent Change in LDL-C from Baseline to Week 104 was reported in this endpoint. Analysis was performed on mITT population. Here, number of subjects analysed = subjects with available data for this endpoint. The on-treatment estimand was analysed using the same imputation model as ITT Estimand, but considered the 'on-treatment' LDL-C values alone for the analysis.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 104 | |

| End point values | OL Period: Placebo/Alirocu mab Q2W | OL Period: Alirocumab Q2W | OL Period: Placebo/Alirocu mab Q4W | OL Period: Alirocumab Q4W |
|-------------------------------------|--|---------------------------------|--|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 45 | 23 | 47 |
| Units: percent change | | | | |
| least squares mean (standard error) | -22.8 (± 5.1) | -25.8 (± 4.9) | -27.6 (± 7.6) | -23.4 (± 4.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cogstate Battery Test - Overall Composite Score at Weeks 24, 68 and 104

| | |
|--|---|
| End point title | Change From Baseline in Cogstate Battery Test - Overall Composite Score at Weeks 24, 68 and 104 |
| End point description: | |
| Cogstate battery test (cognitive testing system) consisted of detection test (DET), identification test (IDN), one card learning test (OCL) and Groton maze learning test (GML) to assess processing speed, attention, visual learning and executive functioning, respectively. For each test, Z-scores were computed based on subject's age at Baseline and Weeks 24, 68 and 104. Composite score: mean of Z-scores equally weighted, provided that at least 3 of 4 tests were available and if all of these domains were covered as: attention, through either DET or IDN, visual learning, through OCL and executive function, through GML. There is not minimum/maximum since values were reported as z-score but z-score of 0 means result equals to mean with negative numbers indicating values lower than mean and positive values higher. Positive change in z-score = improvement in cognition (i.e., better outcome) and negative change in z-score = worsening in cognition (i.e., worse outcome). n = subjects with data. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 24, 68 and 104 | |

| End point values | Placebo/Alirocumab Q2W | Alirocumab Q2W | Placebo/Alirocumab Q4W | Alirocumab Q4W |
|--------------------------------------|------------------------|----------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[57] | 49 ^[58] | 27 ^[59] | 52 ^[60] |
| Units: Z-score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 24 (n = 16, 24, 16, 29) | -0.403 (± 1.008) | -0.313 (± 0.444) | -0.218 (± 0.501) | -0.136 (± 0.637) |
| Week 68 (n = 13, 23, 16, 28) | -0.421 (± 1.752) | -0.334 (± 0.912) | -0.272 (± 0.814) | -0.263 (± 0.717) |
| Week 104 (n = 13, 21, 15, 22) | -0.601 (± 1.612) | -0.439 (± 0.917) | -0.393 (± 0.764) | -0.638 (± 0.791) |

Notes:

[57] - Safety population: randomised population who had actually taken at least 1 dose/partial dose of IMP.

[58] - Analysis was performed on safety population.

[59] - Analysis was performed on safety population.

[60] - Analysis was performed on safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Tanner Staging at Baseline and Weeks 24, 68 and 104

| | |
|---|---|
| End point title | Number of Subjects With Tanner Staging at Baseline and Weeks 24, 68 and 104 |
| End point description: | |
| Tanner stage defines physical measurements of development in children and adolescent based on external primary and secondary sex characteristics. Subjects were evaluated for pubic hair distribution, breast development (only females) and genital development (only males) and classified in 3 categories as: Prepubescent (defined as a person just before start of the development of adult sexual characteristics), Pubescent (defined as a person at or approaching the age of puberty), Postpubescent (sexually mature or a person who has completed puberty). Analysis was performed on safety population. Here, 'n' = subjects with available data for each specified category. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 24, 68 and 104 | |

| End point values | Placebo/Alirocumab Q2W | Alirocumab Q2W | Placebo/Alirocumab Q4W | Alirocumab Q4W |
|---|------------------------|----------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 | 49 | 27 | 52 |
| Units: subjects | | | | |
| Baseline: Boys - Prepubescent (n=17, 19, 12, 18) | 1 | 4 | 5 | 0 |
| Baseline: Boys - Pubescent (n=17, 19, 12, 18) | 13 | 13 | 4 | 14 |
| Baseline: Boys - Postpubescent (n=17, 19, 12, 18) | 3 | 2 | 3 | 4 |
| Baseline: Girls - Prepubescent (n=8, 30, 15, 34) | 1 | 4 | 1 | 7 |
| Baseline: Girls - Pubescent (n=8, 30, 15, 34) | 6 | 16 | 8 | 13 |
| Baseline: Girls - Postpubescent (n=8, 30, 15, 34) | 1 | 10 | 6 | 14 |
| Week 24: Boys - Prepubescent (n=17, 17, 11, 17) | 0 | 3 | 1 | 0 |
| Week 24: Boys - Pubescent (n=17, 17, 11, 17) | 13 | 11 | 7 | 12 |
| Week 24: Boys - Postpubescent (n=17, 17, 11, 17) | 4 | 3 | 3 | 5 |
| Week 24: Girls - Prepubescent (n=8, 28, 12, 27) | 1 | 4 | 1 | 2 |
| Week 24: Girls - Pubescent (n=8, 28, 12, 27) | 5 | 15 | 6 | 16 |
| Week 24: Girls - Postpubescent (n=8, 28, 12, 27) | 2 | 9 | 5 | 9 |
| Week 68: Boys - Prepubescent (n=11, 16, 9, 15) | 0 | 1 | 1 | 0 |
| Week 68: Boys - Pubescent (n=11, 16, 9, 15) | 7 | 9 | 5 | 9 |
| Week 68: Boys - Postpubescent (n=11, 16, 9, 15) | 4 | 6 | 3 | 6 |
| Week 68: Girls - Prepubescent (n=7, 26, 11, 26) | 0 | 3 | 1 | 1 |
| Week 68: Girls - Pubescent (n=7, 26, 11, 26) | 6 | 14 | 5 | 16 |
| Week 68: Girls - Postpubescent (n=7, 26, 11, 26) | 1 | 9 | 5 | 9 |
| Week 104: Boys - Prepubescent (n=13, 15, 8, 15) | 0 | 1 | 1 | 0 |
| Week 104: Boys - Pubescent (n=13, 15, 8, 15) | 6 | 8 | 5 | 8 |
| Week 104: Boys - Postpubescent (n=13, 15, 8, 15) | 7 | 6 | 2 | 7 |
| Week 104: Girls - Prepubescent (n=6, 21, 11, 29) | 0 | 0 | 1 | 1 |
| Week 104: Girls - Pubescent (n=6, 21, 11, 29) | 4 | 10 | 5 | 17 |
| Week 104: Girls - Postpubescent (n=6, 21, 11, 29) | 2 | 11 | 5 | 11 |

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Subjects With Treatment-Emergent (TE) Positive Anti-Alirocumab Antibodies (ADA) Response

| | |
|-----------------|---|
| End point title | DB Period: Number of Subjects With Treatment-Emergent (TE) Positive Anti-Alirocumab Antibodies (ADA) Response |
|-----------------|---|

End point description:

ADA samples: analysed using validated non-quantitative, titer-based bridging immunoassay. Number of subjects with positive (+ve) ADA during 24-week treatment period is reported. Treatment-emergent positive ADA response was defined as 1) subjects with no ADA +ve response at Baseline but with any +ve response in post-baseline period or 2) subjects with a +ve ADA response at Baseline and at least a 4- fold increase in titer in the post-baseline period. Persistent +ve response: TE ADA +ve response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period. Persistent +ve response was only analysed for subjects with +ve TE ADA response. ADA population: all randomised and treated (who actually received at least 1 dose/part of dose of IMP) subjects with available ADA sample at Baseline (Week 0) and at least 1 non-missing ADA sample post first IMP injection and up to Week 24.early termination. 'n'= subject with data and '9999' = no subjects were evaluable.

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

End point timeframe:

Up to 24 weeks

| End point values | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W | DB Period: Alirocumab Q4W |
|---|---------------------------|---------------------------------|---------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 48 | 26 | 49 |
| Units: subjects | | | | |
| TE ADA positive response (n=25, 48, 26, 49) | 0 | 3 | 0 | 0 |
| Persistent positive response (n=0, 3, 0, 0) | 9999 | 0 | 9999 | 9999 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB period: for subjects moved into OL period (OLP), from 1st DB dose up to day before 1st OL dose (till Week[W] 24) & for subjects did not begin OLP, from 1st DB dose up to W24+10 weeks (till W34); OLP: from 1st dose up to last dose+10 weeks (till W112)

Adverse event reporting additional description:

Reported AEs were AEs which developed, worsened/became serious in each of the study periods, i.e. DB and OL, respectively.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | DB Period: Placebo Q2W |
|-----------------------|------------------------|

Reporting group description:

Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q2W for 24 weeks in DB treatment period along with LMT.

| | |
|-----------------------|---------------------------|
| Reporting group title | DB Period: Alirocumab Q2W |
|-----------------------|---------------------------|

Reporting group description:

Subjects received SC injection of alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W for 24 weeks in DB treatment period along with LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8.

| | |
|-----------------------|------------------------|
| Reporting group title | DB Period: Placebo Q4W |
|-----------------------|------------------------|

Reporting group description:

Subjects received SC injection of placebo (matched to alirocumab) based on their BW (<50 kg or ≥50 kg) Q4W for 24 weeks in DB treatment period along with LMT.

| | |
|-----------------------|---------------------------|
| Reporting group title | DB Period: Alirocumab Q4W |
|-----------------------|---------------------------|

Reporting group description:

Subjects received SC injection of alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W for 24 weeks in DB treatment period along with LMT. Alirocumab dose was up-titrated to 75 mg or 150 mg Q2W from Week 12, when LDL-C level ≥110 mg/dL (2.85 mmol/L) at Week 8.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | OL Period: Placebo/Alirocumab Q2W |
|-----------------------|-----------------------------------|

Reporting group description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) Q2W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|-----------------------|---------------------------|
| Reporting group title | OL Period: Alirocumab Q2W |
|-----------------------|---------------------------|

Reporting group description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 40 mg (for BW <50 kg) or 75 mg (for BW ≥50 kg) from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 40 mg to 75 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 40 mg to 75 mg (for BW <50 kg) or 75 mg to 150 mg (for BW ≥50 kg) or down titrated as 75 mg to 40 mg (for BW <50 kg) or 150 mg to 75 mg (for BW ≥50 kg).

| | |
|-----------------------|-----------------------------------|
| Reporting group title | OL Period: Placebo/Alirocumab Q4W |
|-----------------------|-----------------------------------|

Reporting group description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based

on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

| | |
|-----------------------|---------------------------|
| Reporting group title | OL Period: Alirocumab Q4W |
|-----------------------|---------------------------|

Reporting group description:

After completion of DB treatment period, eligible subjects entered into OL treatment period and received alirocumab 150 mg (for BW <50 kg) or 300 mg (for BW ≥50 kg) Q4W from Week 24 up to an additional 80 weeks (i.e., up to Week 104) added to stable LMT. After Week 24, dose up-titrated from 150 mg to 300 mg when BW increased from <50 kg to ≥50 kg. From Week 32 up to Week 104, based on subject LDL-C value, alirocumab dose was either up-titrated as 150 mg Q4W to 75 mg Q2W (for BW <50 kg) or 300 mg Q4W to 150 mg Q2W (for BW ≥50 kg) or down titrated as 75 mg Q2W to 40 mg Q2W (for BW <50 kg) or 150 mg Q2W to 75 mg Q2W (for BW ≥50 kg).

| Serious adverse events | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W |
|---|---------------------------|------------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 4 / 49 (8.16%) | 1 / 27 (3.70%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Ligament Rupture | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina Pectoris | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Syncope | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus Urinary | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Major Depression | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | 0 / 27 (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 | | | |
| Sympathetic Posterior Cervical Syndrome | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|----------------|----------------|----------------|
| Appendicitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 49 (0.00%) | 0 / 27 (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 |
| Pharyngitis Streptococcal | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | DB Period: Alirocumab Q4W | OL Period: Placebo/Alirocumab Q2W | OL Period: Alirocumab Q2W |
|---|------------------------------|---|------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 25 (0.00%) | 4 / 46 (8.70%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Ligament Rupture | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina Pectoris | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 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 | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus Urinary | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Major Depression | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Sympathetic Posterior Cervical Syndrome | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis Streptococcal | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 1 / 46 (2.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | OL Period: Placebo/Alirocumab Q4W | OL Period: Alirocumab Q4W | |
|---|---|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 3 / 49 (6.12%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Ligament Rupture | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina Pectoris | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus Urinary | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Major Depression | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Sympathetic Posterior Cervical Syndrome | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis Streptococcal | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | DB Period: Placebo Q2W | DB Period: Alirocumab Q2W | DB Period: Placebo Q4W |
|---|------------------------|---------------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 25 (36.00%) | 15 / 49 (30.61%) | 8 / 27 (29.63%) |
| Investigations | | | |
| Low Density Lipoprotein Decreased | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 3 / 49 (6.12%) 3 | 1 / 27 (3.70%) 1 |
| Migraine subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 49 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| General disorders and administration site conditions Injection Site Reaction subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 3 / 49 (6.12%) 12 | 0 / 27 (0.00%) 0 |
| Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 49 (0.00%) 0 | 2 / 27 (7.41%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 49 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal Pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 49 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Infections and infestations Covid-19 subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 49 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 7 / 49 (14.29%) 7 | 2 / 27 (7.41%) 2 |
| Tonsillitis subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 3 / 49 (6.12%) 3 | 1 / 27 (3.70%) 1 |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 3 / 49 (6.12%) 3 | 3 / 27 (11.11%) 3 |

| | | | |
|--|------------------------------|---|------------------------------|
| Non-serious adverse events | DB Period: Alirocumab Q4W | OL Period: Placebo/Alirocumab Q2W | OL Period: Alirocumab Q2W |
| Total subjects affected by non-serious | | | |

| | | | |
|--|------------------|-----------------|------------------|
| adverse events | | | |
| subjects affected / exposed | 10 / 52 (19.23%) | 9 / 25 (36.00%) | 12 / 46 (26.09%) |
| Investigations | | | |
| Low Density Lipoprotein Decreased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 25 (8.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 1 / 25 (4.00%) | 5 / 46 (10.87%) |
| occurrences (all) | 5 | 6 | 5 |
| Migraine | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Injection Site Reaction | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 25 (4.00%) | 3 / 46 (6.52%) |
| occurrences (all) | 3 | 2 | 17 |
| Gastrointestinal disorders | | | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 2 / 25 (8.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 4 / 46 (8.70%) |
| occurrences (all) | 0 | 0 | 4 |
| Infections and infestations | | | |
| Covid-19 | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 1 / 46 (2.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 2 / 25 (8.00%) | 3 / 46 (6.52%) |
| occurrences (all) | 4 | 2 | 5 |
| Tonsillitis | | | |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 25 (0.00%) | 0 / 46 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 2 / 25 (8.00%) | 2 / 46 (4.35%) |
| occurrences (all) | 3 | 2 | 4 |

| Non-serious adverse events | OL Period: Placebo/Alirocumab Q4W | OL Period: Alirocumab Q4W | |
|---|---|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 25 (24.00%) | 15 / 49 (30.61%) | |
| Investigations | | | |
| Low Density Lipoprotein Decreased | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 49 (4.08%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 7 / 49 (14.29%) | |
| occurrences (all) | 5 | 15 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Injection Site Reaction | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|----------------|----------------|--|
| Covid-19 | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 4 / 49 (8.16%) | |
| occurrences (all) | 1 | 5 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 3 / 49 (6.12%) | |
| occurrences (all) | 2 | 5 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 49 (4.08%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 02 January 2019 | <p>The following changes were done:</p> <ul style="list-style-type: none">- Added Q4W efficacy evaluation in primary objectives.- Updated DB treatment period with dosing regimen of Q4W (alirocumab 150 mg and 300 mg; n~75 subjects) and number of enrolled subjects in Q2W dosing regimen would be administered study treatment (alirocumab 40 mg and 75 mg was changed to approximately half; n~75).- Description of Q4W dosing regimen and information on maintaining the blind was added for subjects in Q4W dosing regimen to indicate administration of alirocumab every 4 weeks during first 12 weeks and then after Week 12 administration of alirocumab Q4W alternating with placebo Q4W in order to maintain blind at time of possible dose-adjustment.- Dose-adjustment information at Week 24 and from Week 32 was added for subjects enrolled Q4W dosing regimen.- Added 1 mL of alirocumab 150 mg/mL solution for 150 mg dose.- Information of Q4W dose used added: alirocumab 150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg.- Revised statistical analysis: sample size determination and addition of alirocumab Q4W and placebo Q4W to treatment groups to be analysed.- Described sample size calculations and considerations for Q2W and Q4W dosing regimens.- Added duration of exposure description for Q4W dosing regimen.- Revised and described handling of multiplicity.- Graphical study design for Q4W dosing regimen was added as Flow chart.- Added clinical information of the additional cohort (Cohort 4) conducted with Q4W dosing regimen in the DFI14223 that support the evaluation of the Q4W dosing regimen in EFC14643 study.- Corrected Q2W dose-adjustment according to BW as per Investigator's judgment.- Added information on fact that from total number of 150 subjects, half of those would enrolled in each dosing regimen.- Minor editorial revisions were done.- Clarified that all countries were allowed to perform monthly urine pregnancy tests, in keeping with clinical trial facilitation guidelines. |

| | |
|-----------------|---|
| 06 January 2021 | <p>The following changes were done:</p> <ul style="list-style-type: none"> - Updated to clarify that Investigator was able to adjust dose of alirocumab, for increasing the efficacy or purpose of subject safety. - Revised in order to specify analysing each of two randomised dosing regimen cohorts separately (use of the contemporaneously randomised placebo group for each dosing regimen cohort (Q2W, Q4W) instead of combined placebo group). - Revised the comparisons and of statistical models (a separate model would be run for each dosing regimen cohort). - To be consistent with two-sided test with significance level of 2.5%, 97.5% CI would be computed instead of 95% CI for primary and secondary efficacy endpoints. - Revised treatment groups to be displayed in safety result summaries: by treatment groups within each dosing regimen cohort; and by treatment group regardless of dosing regimen cohorts (pooled across cohorts). - Added details to clarify two-step analysis process at the completion of double-blind treatment period and whole study, respectively. - Updated IRT listings. - Changed the description of process for the management of complementary source documents. - Update added for clarity of multiplicity. - Added the definition of the treatment period for the Q4W dosing regimen cohort. - Revised the treatment groups to be displayed in accordance with safety summaries. - Defined & clarified two-step analysis. - Included the possibility to perform remote monitoring in the context of regional or national emergency such as the current coronavirus disease (COVID-19) pandemic. - Added the dosing regimen cohort and treatment-by-dosing regimen cohort effects in the statistical model. - The use of the multiple imputations process was removed. - Added contingency measures for a regional or national emergency that can be declared by a governmental agency such as the current COVID-19 pandemic. - Minor grammatical & editorial revisions. - Added word "cohort" at relevant places. |
|-----------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported