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 NO
Global end of trial date	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	• 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)	EMEA-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 ± 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 [>=] 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 alirocumab) 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 alirocumab) 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 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.

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
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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 uptitrated 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	13.1		
standard deviation	± 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	176.79		
standard deviation	± 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 uptitrated 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 DFI14223 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 (± 3.9)	-31.0 (± 3.2)	-3.7 (± 4.0)	-35.6 (± 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 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[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 (± 3.1)	-30.0 (± 2.5)	1.1 (± 3.2)	-31.7 (± 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 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).

[24] - Threshold for significance at 0.025 level.

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 (± 2.9)	-25.3 (± 2.2)	0.9 (± 2.5)	-27.0 (± 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 (± 5.9)	-12.7 (± 3.9)	-2.5 (± 6.9)	-16.0 (± 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 mode, 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/Alirocumab Q2W	OL Period: Alirocumab Q2W	OL Period: Placebo/Alirocumab 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/Alirocumab Q2W	OL Period: Alirocumab Q2W	OL Period: Placebo/Alirocumab 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 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	2 / 25 (8.00%)	3 / 49 (6.12%)	1 / 27 (3.70%)
occurrences (all)	2	3	1
Migraine			
subjects affected / exposed	2 / 25 (8.00%)	0 / 49 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Injection Site Reaction			
subjects affected / exposed	0 / 25 (0.00%)	3 / 49 (6.12%)	0 / 27 (0.00%)
occurrences (all)	0	12	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 25 (0.00%)	0 / 49 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 49 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 49 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 25 (0.00%)	0 / 49 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	7 / 49 (14.29%)	2 / 27 (7.41%)
occurrences (all)	2	7	2
Tonsillitis			
subjects affected / exposed	1 / 25 (4.00%)	3 / 49 (6.12%)	1 / 27 (3.70%)
occurrences (all)	1	3	1
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 25 (12.00%)	3 / 49 (6.12%)	3 / 27 (11.11%)
occurrences (all)	3	3	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	The following changes were done: - 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	The following changes were done: - 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