Clinical trial results:
A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab Versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk with Non-HDL-C Not Adequately Controlled with Maximally Tolerated Statin Therapy

Summary

EudraCT number	2015-001934-19
Trial protocol	FI DE GB SE IT
Global end of trial date	15 May 2017
Results information	
Result version number	v1 (current)
This version publication date	27 May 2018
First version publication date	27 May 2018

Trial information

Trial identification	
Sponsor protocol code	LPS14354
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02642159
WHO universal trial number (UTN)	U1111-1172-5262

Notes:

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

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-high-density lipoprotein cholesterol (non-HDL-C) after 24 weeks of treatment in subjects with type 2 diabetes (T2DM) and mixed dyslipidemia at high cardiovascular risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy.

Protection of trial subjects:

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

Background therapy:

All subjects received stable antihyperglycemic drugs (including insulin), stable dose of statin without other lipid modifying therapy (LMT) as clinically indicated (except ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid allowed for usual care arm) throughout the duration of study.

Evidence for comparator: -

Actual start date of recruitment	15 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United Arab Emirates: 2
Country: Number of subjects enrolled	United States: 233
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Sweden: 4

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	Germany: 33
Worldwide total number of subjects	413
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	216
From 65 to 84 years	194
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 119 centers in 15 countries. A total of 864 subjects were screened between March 2016 and September 2016, 451 of whom were screen failures. Screen failures were mainly due to inclusion criteria not met.

Pre-assignment

Screening details:

Randomization was stratified by investigator's choice of usual care therapy, which was pre-specified prior to randomization. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 2:1 ratio (alirocumab: usual care) after confirmation of selection criteria. 413 subjects were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W

Arm description:

Alirocumab 75 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without other LMT for 24 weeks. Alirocumab dose uptitrated to 150 mg Q2W from Week 12 when non-HDLC levels >=100 mg/dL (2.59 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:

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

Arm title	Usual Care

Arm description:

Subjects on usual care continued on antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without additional LMT or with either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid as per Investigator's judgment for 24 weeks.

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

Dosage and administration details:

Ezetimibe was administered as per Investigator's judgment for 24 weeks.

Investigational medicinal product name	Fenofibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use
Dosage and administration details:	
Fenofibrate was administered as per Investigator’s judgment for 24 weeks.	
Investigational medicinal product name	Nicotinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Nicotinic acid was administered as per Investigator’s judgment for 24 weeks.	
Investigational medicinal product name	Omega-3 fatty acids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Omega-3 fatty acids were administered as per Investigator’s judgment for 24 weeks.	

Number of subjects in period 1	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care
Started	276	137
Treated (Safety Population)	275	137
ITT Population	273	136
ITT: Intent to Prescribe Fenofibrate	47 [1]	24 [2]
Completed	245	129
Not completed	31	8
Other than specified above	10	3
Adverse Event	10	4
Randomized but not treated	1	-
Withdrawal by Subject	9	1
Poor compliance to study protocol	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestone represents only those randomised subjects who were included in ITT: Intent to Prescribe Fenofibrate statum. Fenofibrate was only ‘intended to prescribe’ in the Alirocumab arm but not actually administered.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestone represents only those randomised subjects who were included in ITT: Intent to Prescribe Fenofibrate statum.

Baseline characteristics

Reporting groups	
Reporting group title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W
Reporting group description:	
Alirocumab 75 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without other LMT for 24 weeks. Alirocumab dose uptitrated to 150 mg Q2W from Week 12 when non-HDLC levels >=100 mg/dL (2.59 mmol/L) at Week 8.	
Reporting group title	Usual Care
Reporting group description:	
Subjects on usual care continued on antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without additional LMT or with either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid as per Investigator's judgment for 24 weeks.	

Reporting group values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care	Total
Number of subjects	276	137	413
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.8	64.1	
standard deviation	± 9.3	± 8.8	-
Gender categorical Units: Subjects			
Female	129	68	197
Male	147	69	216
Ethnicity Units: Subjects			
Hispanic or Latino	35	14	49
Not Hispanic or Latino	240	123	363
Unknown or Not Reported	1	0	1
Race Units: Subjects			
White/Caucasian	247	123	370
Black	16	6	22
Asian/Oriental	3	7	10
American Indian or Alaska Native	4	0	4
Native Hawaiian or Other Pacific Islander	0	0	0
Other	6	1	7
Intent to Prescribe Treatment			
Randomization was stratified by the Investigator’s selection of usual care therapy prior to randomization. LMTs were only ‘intended to prescribe’ in the Alirocumab arm but not actually administered.			
Units: Subjects			
Fenofibrate	48	24	72
No additional LMT	79	39	118
Ezetimibe	104	52	156

Omega-3 fatty acids	43	21	64
Nicotinic acid	2	1	3

Non-HDL-C in mg/dL			
non-HDL-C = Total cholesterol (Total-C) minus high-density lipoprotein cholesterol (HDL-C)			
Units: mmol/L			
arithmetic mean	155.1	161.5	
standard deviation	± 46.2	± 48.8	-
Non-HDL-C in mmol/L			
non-HDL-C = Total-C minus HDL-C			
Units: mmol/L			
arithmetic mean	4.0	4.2	
standard deviation	± 1.2	± 1.2	-

End points

End points reporting groups

Reporting group title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W

Reporting group description:

Alirocumab 75 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without other LMT for 24 weeks. Alirocumab dose uptitrated to 150 mg Q2W from Week 12 when non-HDLC levels >=100 mg/dL (2.59 mmol/L) at Week 8.

Reporting group title	Usual Care

Reporting group description:

Subjects on usual care continued on antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without additional LMT or with either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid as per Investigator's judgment for 24 weeks.

Subject analysis set title	Usual Care: Intent to Prescribe Fenofibrate
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects on usual care continued on antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy with fenofibrate as per Investigator's judgment for 24 weeks.

Primary: Percent Change From Baseline in Non-HDL-C at Week 24: Overall Intent-to-treat (ITT) Analysis

End point title	Percent Change From Baseline in Non-HDL-C at Week 24: Overall Intent-to-treat (ITT) Analysis

End point description:

Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment.

End point type	Primary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-37.3 (± 3.0)	-4.7 (± 3.3)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

Alirocumab group was compared to usual care group using an appropriate contrast statement.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care

Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-38.1
upper limit	-27

Notes:

[1] - Threshold for significance <=0.025.

Primary: Percent Change From Baseline in Non-HDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Non-HDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum[2]

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

From Baseline to Week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-41.7 (± 3.4)	-8.5 (± 4.8)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe : Statistical Comparison

Statistical analysis description:

Alirocumab group was compared to usual care group for the intent to prescribe fenofibrate using an appropriate contrast statement.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-33.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-46.6
upper limit	-19.9

Notes:

[3] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Measured Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24: Overall ITT Analysis

End point title	Percent Change From Baseline in Measured Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24: Overall ITT Analysis

End point description:

Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline LDL-C value on-or off-treatment (LDL-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-43.3 (± 3.6)	-0.3 (± 4.0)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses for overall ITT analysis. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care

Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-43
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-49.7
upper limit	-36.3

Notes:

[4] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Measured LDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Measured LDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum[5]

End point description:

Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. LDL-C ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-47.0 (± 4.2)	8.7 (± 5.8)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe : Statistical Comparison

Statistical analysis description:

A separate hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses for ITT-intent to prescribe fenofibrate stratum. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.025 level.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-55.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-71.8
upper limit	-39.6

Notes:

[6] - Threshold for significance <=0.025.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-35.5 (± 2.9)	-9.4 (± 3.2)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-26.1

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-31.5
upper limit	-20.7

Notes:

[7] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Non-HDL-C at Week 12: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Non-HDL-C at Week 12: ITT- Intent to Prescribe Fenofibrate Stratum[8]

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-34.7 (± 3.2)	-7.3 (± 4.5)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe : Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.4

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-40
upper limit	-14.8

Notes:

[9] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Measured LDL-C at Week 12: Overall ITT Analysis

End point title	Percent Change From Baseline in Measured LDL-C at Week 12: Overall ITT Analysis

End point description:

Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. LDL-C ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-41.7 (± 3.3)	-7.0 (± 3.6)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-34.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-40.8
upper limit	-28.6

Notes:

[10] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Measured LDL-C at Week 12: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Measured LDL-C at Week 12: ITT- Intent to Prescribe Fenofibrate Stratum[11]

End point description:

Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. LDL-C ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-44.3 (± 3.6)	5.4 (± 5.1)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe : Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-49.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-63.7
upper limit	-35.8

Notes:

[12] - Threshold for significance <=0.025.

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

End point title	Percent Change From Baseline in Apolipoprotein B (Apo-B) at Week 24: Overall ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline Apo-B value on-or off-treatment (Apo-B ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-33.8 (± 2.7)	-1.6 (± 3.0)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-32.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-37.3
upper limit	-27.2

Notes:

[13] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Apo-B at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Apo-B at Week 24: ITT-Intent to Prescribe Fenofibrate Stratum[14]

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. Apo-B ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-38.9 (± 3.1)	-3.8 (± 4.4)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe: Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-47.4
upper limit	-22.9

Notes:

[15] - Threshold for significance <=0.025.

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

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 : Overall ITT Analysis

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline Total-C value on- or off-treatment (Total-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	-27.4 (± 2.3)	-2.8 (± 2.5)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-28.8
upper limit	-20.3

Notes:

[16] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Total-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Total-C at Week 24: ITT-Intent to Prescribe Fenofibrate Stratum[17]

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. Total-C ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	-30.9 (± 2.6)	-5.7 (± 3.7)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe: Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-35.4
upper limit	-15.1

Notes:

[18] - Threshold for significance <=0.025.

Secondary: Percent Change From Baseline in Lipoprotein(a) at Week 24 : Overall ITT Analysis

End point title	Percent Change From Baseline in Lipoprotein(a) at Week 24 : Overall ITT Analysis

End point description:

Adjusted means and standard errors at Week 24 were obtained from multiple imputation approach followed by robust regression model for handling of missing data. All available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment were included in the imputation model. ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
arithmetic mean (standard error)	-23.7 (± 1.9)	3.7 (± 2.6)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-27.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-34.6
upper limit	-20.1

Notes:

[19] - Threshold for significance <=0.025. Multiple imputation approach followed by robust regression model.

Secondary: Percent Change From Baseline in Lipoprotein(a) at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Lipoprotein(a) at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum[20]

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

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

Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
arithmetic mean (standard error)	-18.9 (± 4.4)	3.9 (± 6.6)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe: Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [21]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-22.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-40.6
upper limit	-5

Notes:

[21] - Threshold for significance <=0.025. Multiple imputation approach followed by robust regression model.

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

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 24: Overall ITT Analysis

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
arithmetic mean (standard error)	-13.0 (± 2.0)	-8.8 (± 2.8)		

Statistical analyses

Statistical analysis title	Overall ITT: Statistical Comparison

Statistical analysis description:

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

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2191 [22]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-4.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-11.8
upper limit	3.4

Notes:

[22] - Threshold for significance <=0.025. Multiple imputation approach followed by robust regression.

Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum[23]

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
arithmetic mean (standard error)	-15.4 (± 4.7)	-24.4 (± 6.6)		

Statistical analyses

Statistical analysis title	ITT- Intent to Prescribe: Statistical Comparison

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint of ITT-intent to prescribe fenofibrate stratum was statistically significant).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W v Usual Care: Intent to Prescribe Fenofibrate
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2651 [24]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-9.1
upper limit	27.1

Notes:

[24] - Threshold for significance <=0.025. Multiple imputation approach followed by robust regression.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment (HDL-C ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Percent change				
least squares mean (standard error)	14.5 (± 2.5)	8.2 (± 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in HDL-C at Week 24: ITT-Intent to Prescribe Fenofibrate Stratum[25]

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. HDL-C ITT population. Here, 'Number of subjects analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	47	24		
Units: Percent change				
least squares mean (standard error)	13.5 (± 2.9)	12.3 (± 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL-C Particle Number at Week 24: Overall ITT Analysis

End point title	Percent Change From Baseline in LDL-C Particle Number at Week 24: Overall ITT Analysis

End point description:

LDL-C particle number was calculated from lipid subfractions by nuclear magnetic resonance (NMR) spectroscopy. Adjusted LS means and standard errors at Week 24 from MMRM model including all

available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline LDL-C particle number on- or off-treatment (LDL-C particle number ITT population).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	135		
Units: Percent change				
least squares mean (standard error)	-41.6 (± 3.0)	-3.9 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL-C Particle Number at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

End point title	Percent Change From Baseline in LDL-C Particle Number at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum[26]

End point description:

LDL-C particle number was calculated from lipid subfractions by NMR spectroscopy. Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 8 to Week 24 regardless of status on- or off-treatment in the intent to prescribe fenofibrate stratum. The usual care here corresponds to fenofibrate. LDL-C particle number ITT population. Here, 'Number of subjects
analyzed' = subjects from intent to prescribe fenofibrate stratum who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care: Intent to Prescribe Fenofibrate		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	24		
Units: Percent change				
least squares mean (standard error)	-45.4 (± 3.5)	-2.9 (± 5.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Hemoglobin A1c (HbA1c) at Week 12 and 24 : Overall ITT Analysis

End point title	Absolute Change From Baseline in Hemoglobin A1c (HbA1c) at Week 12 and 24 : Overall ITT Analysis

End point description:

Absolute change = HbA1c value at specified week minus HbA1c value at baseline. ITT population. Here, 'n' signifies number of subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: mmol/mol				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 265, 133)	0.59 (± 6.82)	0.43 (± 5.70)		
Change at Week 24 (n= 251, 128)	2.84 (± 8.04)	2.40 (± 8.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Fasting Plasma Glucose (FPG) at Week 12 and 24 : Overall ITT Analysis

End point title	Absolute Change From Baseline in Fasting Plasma Glucose (FPG) at Week 12 and 24 : Overall ITT Analysis

End point description:

Absolute change = FPG value at specified week minus FPG value at baseline. ITT population. Here, 'n' signifies number of subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: mmol/L				
arithmetic mean (standard deviation)				
Change at Week 12 (n=262, 133)	0.45 (± 2.43)	0.21 (± 1.86)		
Change at Week 24 (n=251, 128)	0.68 (± 2.54)	0.03 (± 2.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Number of Glucose-Lowering Treatments at Week 12 and 24 : Overall ITT Analysis

End point title	Absolute Change From Baseline in Number of Glucose-Lowering Treatments at Week 12 and 24 : Overall ITT Analysis

End point description:

Glucose lowering treatment was calculated for non-insulin treatments as one for each unique treatment received and for insulin treatment as one in total for all subjects who have taken one or more treatments. Absolute change = number of glucose-lowering treatments at specified week minus baseline value. ITT population. Here, 'n' signifies number of subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	136		
Units: Glucose lowering treatments				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 271, 136)	0.04 (± 0.30)	0.04 (± 0.19)		
Change at Week 24 (n=267, 135)	0.07 (± 0.37)	0.04 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 32) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that are AEs that developed/worsened and death that occurred during the 'treatment-emergent period' (the time from the first dose of study drug up to the last dose of study drug +70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W

Reporting group description:

Alirocumab 75 mg SC injection Q2W added to antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without other LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when non- HDL-C levels >=100 mg/dL (2.59 mmol/L) at Week 8.

Reporting group title	Usual Care

Reporting group description:

Subjects on usual care continued on antihyperglycemic drugs (including insulin), stable maximally tolerated dose of statin therapy without additional LMT or with either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid as per Investigator's judgment for 24 weeks.

Serious adverse events	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 275 (9.45%)	12 / 137 (8.76%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Neoplasm			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 275 (0.73%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal Prolapse			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I Disorder			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower Limb Fracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 275 (0.36%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	3 / 275 (1.09%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			

subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	2 / 275 (0.73%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Glaucoma			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			

subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Osteoarthritis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic Foot Infection			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 275 (0.73%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 275 (0.36%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 275 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Usual Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 275 (13.45%)	27 / 137 (19.71%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 275 (5.09%)	9 / 137 (6.57%)	
occurrences (all)	18	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 275 (2.18%)	8 / 137 (5.84%)	
occurrences (all)	6	9	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 275 (1.82%)	7 / 137 (5.11%)	
occurrences (all)	5	7	
Urinary Tract Infection			
subjects affected / exposed	15 / 275 (5.45%)	5 / 137 (3.65%)	
occurrences (all)	15	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported