Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Insulin Treated Patients With Type 1 or Type 2 Diabetes and With Hypercholesterolemia at High Cardiovascular Risk not Adequately Controlled on Maximally Tolerated LDL-C Lowering Therapy

Summary

EudraCT number	2015-000799-92
Trial protocol	GB ES DE NL AT FR BE IT
Global end of trial date	03 April 2017

Results information

Result version number	v1 (current)
This version publication date	15 April 2018
First version publication date	15 April 2018

Trial information

Trial identification

Sponsor protocol code	LPS14355

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02585778
WHO universal trial number (UTN)	U1111-1172-4772

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	28 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 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 placebo in the reduction of calculated low-density lipoprotein cholesterol (LDL-C) after 24 weeks of treatment in subjects with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy.
- To evaluate the safety and tolerability of alirocumab in subjects with diabetes treated with insulin.

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 maximum tolerated dose of statin with or without other lipid-modifying therapy (LMT), insulin alone or with other antihyperglycemic drugs as clinically indicated throughout the duration of study.

Evidence for comparator: -

Actual start date of recruitment	23 October 2015
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	Austria: 12
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 95
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Spain: 69
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	United States: 192
Worldwide total number of subjects	517
EEA total number of subjects	318

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)	277
From 65 to 84 years	238
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 103 sites in 10 countries. Of these, 97 active sites randomized at least 1 subject. Overall 796 subjects were screened between October 2015 and August 2016, of whom 279 were screen failures. Screen failures were mainly due to exclusion criteria met or inclusion criteria not met.

Pre-assignment

Screening details:

Randomization was stratified by diabetes type (Type 1 diabetes mellitus [T1DM] versus Type 2 diabetes mellitus [T2DM]). Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 2:1 ratio (Alirocumab:Placebo). A total of 517 subjects were randomized. Baseline and efficacy data were analyzed per stratum.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

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 stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 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	Placebo Q2W

Arm description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

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

Dosage and administration details:

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

Number of subjects in period 1	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Placebo Q2W
Started	345	172
Treated (Safety Population)	344	170
ITT Population	336	167
mITT Population	333	164
T1DM Subjects	51 [1]	25 [2]
T2DM Subjects	294 [3]	147 [4]
Completed	312	157
Not completed	33	15
Other than specified above	6	2
Adverse Event	17	4
Randomized but not treated	1	2
Death	-	1
Subject did not wish to continue	9	4
Poor compliance to study protocol	-	2

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: T1DM subjects and T2DM subjects are strata of randomized arms. Total subjects of these 2 strata are greater than the number of subjects that completed, minus those who left.

[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: T1DM subjects and T2DM subjects are strata of randomized arms. Total subjects of these 2 strata are greater than the number of subjects that completed, minus those who left.

[3] - 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: T1DM subjects and T2DM subjects are strata of randomized arms. Total subjects of these 2 strata are greater than the number of subjects that completed, minus those who left.

[4] - 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: T1DM subjects and T2DM subjects are strata of randomized arms. Total subjects of these 2 strata are greater than the number of subjects that completed, minus those who left.

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 stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.	
Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.	

Reporting group values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Placebo Q2W	Total
Number of subjects	345	172	517
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62.6	63.2	
standard deviation	± 9.6	± 9.4	-
Gender categorical			
Units: Subjects			
Female	155	77	232
Male	190	95	285
Ethnicity			
Units: Subjects			
Hispanic or Latino	14	8	22
Not Hispanic or Latino	330	163	493
Unknown or Not Reported	1	1	2
Race			
Units: Subjects			
White/Caucasian	309	159	468
Black	28	7	35
Asian/Oriental	7	3	10
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	1	3	4
Calculated LDL-C in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL cholesterol = Total cholesterol - high density lipoprotein [HDL] cholesterol-[Triglyceride/5])			
Units: mg/dL			
arithmetic mean	113.1	109.6	
standard deviation	± 40.7	± 38.0	-
Calculated LDL-C in mmol/L			
Calculated LDL-C in mmol/L from Friedewald formula (LDL cholesterol = Total cholesterol - HDL cholesterol - [Triglyceride/2.2]).			

Units: mmol/L			
arithmetic mean	2.930	2.840	
standard deviation	± 1.053	± 0.984	-

Subject analysis sets

Subject analysis set title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Subject analysis set title	Placebo Q2W: T1DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

Subject analysis set title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Subject analysis set title	Placebo Q2W: T2DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

Reporting group values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects
Number of subjects	51	25	294
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.9	58.5	63.9
standard deviation	± 10.1	± 7.8	± 8.9
Gender categorical			
Units: Subjects			
Female	22	8	133
Male	29	17	161
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	13
Not Hispanic or Latino	50	25	280
Unknown or Not Reported	0	0	1
Race			
Units: Subjects			
White/Caucasian	50	24	259
Black	1	0	27

Asian/Oriental	0	0	7
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	1	1
Calculated LDL-C in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL cholesterol = Total cholesterol - high density lipoprotein [HDL] cholesterol-[Triglyceride/5])			
Units: mg/dL			
arithmetic mean	126.4	110.2	110.8
standard deviation	± 58.2	± 31.2	± 36.5
Calculated LDL-C in mmol/L			
Calculated LDL-C in mmol/L from Friedewald formula (LDL cholesterol = Total cholesterol - HDL cholesterol - [Triglyceride/2.2]).			
Units: mmol/L			
arithmetic mean	3.273	2.853	2.871
standard deviation	± 1.506	± 0.807	± 0.944

Reporting group values	Placebo Q2W: T2DM Subjects		
Number of subjects	147		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.0		
standard deviation	± 9.4		
Gender categorical			
Units: Subjects			
Female	69		
Male	78		
Ethnicity			
Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	138		
Unknown or Not Reported	1		
Race			
Units: Subjects			
White/Caucasian	135		
Black	7		
Asian/Oriental	3		
American Indian or Alaska Native	0		
Native Hawaiian or other Pacific Islander	0		
Other	2		
Calculated LDL-C in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL cholesterol = Total cholesterol - high density lipoprotein [HDL] cholesterol-[Triglyceride/5])			
Units: mg/dL			
arithmetic mean	109.6		
standard deviation	± 39.1		
Calculated LDL-C in mmol/L			

Calculated LDL-C in mmol/L from Friedewald formula (LDL cholesterol = Total cholesterol - HDL cholesterol - [Triglyceride/2.2]).			
Units: mmol/L			
arithmetic mean	2.838		
standard deviation	± 1.013		

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 stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Reporting group title	Placebo Q2W

Reporting group description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

Subject analysis set title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Subject analysis set title	Placebo Q2W: T1DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

Subject analysis set title	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Subject analysis set title	Placebo Q2W: T2DM Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT, insulin alone or with other antihyperglycemic drugs for 24 weeks.

Primary: Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-treat (ITT) Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-treat (ITT) Analysis

End point description:

Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment.

End point type	Primary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
least squares mean (standard error)	-51.8 (± 3.7)	-3.9 (± 5.3)	-48.2 (± 1.6)	0.8 (± 2.2)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects
Statistical analysis description:	
Alirocumab group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-47.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.7
upper limit	-35

Notes:

[1] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects
Statistical analysis description:	
Alirocumab group was compared to placebo group using an appropriate contrast statement.	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.4
upper limit	-43.6

Notes:

[2] - Threshold for significance at 0.05 level.

Primary: Percentage of Subjects Who Experienced Treatment-Emergent Adverse Events (AEs)

End point title	Percentage of Subjects Who Experienced Treatment-Emergent Adverse Events (AEs)[3]

End point description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of study drug up to the last dose of study drug +70 days). Safety population: all randomized subjects who received at least one dose or part of a dose of a study drug (treated).

End point type	Primary

End point timeframe:

From Baseline up to 10 weeks after last study drug administration (maximum of 32 weeks)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety analyses were descriptive in nature.

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Placebo Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	170		
Units: percentage of subjects				
number (not applicable)				
Any AE	64.5	64.1		
Any Serious AE	9.0	9.4		
Any AE leading to death	0	0.6		
Any AE leading to treatment discontinuation	4.9	2.4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - On-Treatment Analysis

End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). Modified ITT population (mITT): all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percent change				
least squares mean (standard error)	-53.8 (± 3.7)	-3.2 (± 5.3)	-50.9 (± 1.6)	0.7 (± 2.2)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level. Hierarchical testing procedure was followed for T1DM and T2DM subjects separately.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-50.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.4
upper limit	-37.9

Notes:

[4] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-51.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.9
upper limit	-46.4

Notes:

[5] - Threshold for significance at 0.05 level.

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

End point title	Percent Change From Baseline in Measured LDL-C at Week 24 - 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 4 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline measured LDL-C value on- or off-treatment (Measured 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	22	277	139
Units: percent change				
least squares mean (standard error)	-49.4 (± 3.7)	-1.1 (± 5.4)	-43.3 (± 1.6)	2.4 (± 2.2)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-48.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.2
upper limit	-35.5

Notes:

[6] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-45.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.9
upper limit	-40.4

Notes:

[7] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment at Week 12 (ITT population at Week 12).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	284	140
Units: percent change				
least squares mean (standard error)	-49.4 (± 3.5)	-4.5 (± 5.0)	-48.8 (± 1.4)	1.4 (± 2.1)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.9
upper limit	-32.8

Notes:

[8] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subject
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-50.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.2
upper limit	-45.3

Notes:

[9] - Threshold for significance at 0.05 level.

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

Analysis

End point title	Percent Change From Baseline in Measured LDL-C at Week 12 - 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 4 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline measured LDL-C value on- or off-treatment at Week 12 (Measured LDL-C ITT population at Week 12).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	22	275	136
Units: percent change				
least squares mean (standard error)	-46.7 (± 3.6)	-4.0 (± 5.1)	-44.8 (± 1.4)	-0.8 (± 2.0)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-42.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.9
upper limit	-30.5

Notes:

[10] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-44.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49
upper limit	-39.2

Notes:

[11] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment (non-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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
least squares mean (standard error)	-45.9 (± 3.3)	-3.2 (± 4.8)	-37.9 (± 1.4)	0.7 (± 2.0)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-42.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.2
upper limit	-31.3

Notes:

[12] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-38.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.4
upper limit	-33.9

Notes:

[13] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	22	279	140
Units: percent change				
least squares mean (standard error)	-39.4 (± 3.0)	-0.4 (± 4.3)	-33.4 (± 1.3)	3.3 (± 1.7)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.4
upper limit	-28.7

Notes:

[14] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects
Statistical analysis description:	
Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).	
Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-36.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.9
upper limit	-32.5

Notes:

[15] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
least squares mean (standard error)	-29.9 (± 2.5)	-0.7 (± 3.6)	-26.8 (± 1.0)	0.8 (± 1.5)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.8
upper limit	-20.7

Notes:

[16] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-27.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.2
upper limit	-24.1

Notes:

[17] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted percentages at Week 24 from multiple imputation approach model including available post-baseline data from Week 4 to Week 24 (i.e. up to 21 days after last injection). mITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percentage of subjects				
number (not applicable)	70.2	5.1	76.4	7.4

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	117
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.1
upper limit	1041.8

Notes:

[18] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	84.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.5
upper limit	196.1

Notes:

[19] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching Calculated LDL-C <50 mg/dL (1.3 mmol/L) at Week 24 - On-Treatment Analysis

End point title	Percentage of Subjects Reaching Calculated LDL-C <50 mg/dL (1.3 mmol/L) at Week 24 - On-Treatment Analysis

End point description:

Adjusted percentages at Week 24 from last observation carried forward (LOCF) approach (for T1DM subjects) and multiple imputation approach model (for T2DM subjects) including available post-baseline data from Week 4 to Week 24 (i.e. up to 21 days after last injection). The maximum likelihood estimate did not exist as response rate was zero in a treatment group of T1DM subjects. mITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percentage of subjects				
number (not applicable)	55.1	0	50.7	2.7

Statistical analyses

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	52.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.6
upper limit	168.3

Notes:

[20] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching Calculated Non-HDL-C <100 mg/dL at Week 24 - On-Treatment Analysis

End point title	Percentage of Subjects Reaching Calculated Non-HDL-C <100 mg/dL at Week 24 - On-Treatment Analysis

End point description:

Adjusted percentages at Week 24 from multiple imputation approach model including available post-baseline data from Week 4 to Week 24 (i.e. up to 21 days after last injection). Subjects of the mITT population with one baseline and at least one post-baseline Non-HDL-C value on-treatment (Non-HDL-C mITT population).

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percentage of subjects				
number (not applicable)	79.0	22.9	70.9	13.8

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	33.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	137.4

Notes:

[21] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	27.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	14.2
upper limit	51.5

Notes:

[22] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching Calculated Non-HDL-C <80 mg/dL at Week 24 - On-Treatment Analysis

End point title	Percentage of Subjects Reaching Calculated Non-HDL-C <80 mg/dL at Week 24 - On-Treatment Analysis

End point description:

Adjusted percentages at Week 24 from multiple imputation approach including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection). Non-HDL-C mITT population.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percentage of subjects				
number (not applicable)	59.6	5.3	52.3	1.7

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [23]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	55.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	473.7

Notes:

[23] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by logistic regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	103.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.6
upper limit	433.1

Notes:

[24] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted means and standard errors at Week 24 were obtained from multiple imputation approach for handling of missing data followed by robust regression model. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were included in the imputation model. ITT 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
arithmetic mean (standard error)	-23.0 (± 3.8)	-4.3 (± 5.3)	-19.0 (± 1.6)	-0.5 (± 2.2)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by robust regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [25]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.4
upper limit	-6

Notes:

[25] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by robust regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.7
upper limit	-13.2

Notes:

[26] - Threshold for significance at 0.05 level.

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
least squares mean (standard error)	11.2 (± 2.4)	7.3 (± 3.5)	8.1 (± 1.0)	3.7 (± 1.4)

Statistical analyses

Statistical analysis title	Alirocumab:T1DM Subjects vs. Placebo:T1DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects v Placebo Q2W: T1DM Subjects
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3434 [27]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	12

Notes:

[27] - Threshold for significance at 0.05 level.

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum).

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v

	Placebo Q2W: T2DM Subjects
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [28]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	7.7

Notes:

[28] - Threshold for significance at 0.05 level.

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

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

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach for handling of missing data followed by robust regression model including all available post-baseline data from Week 4 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percent change				
arithmetic mean (standard error)	-13.6 (± 4.7)	1.9 (± 6.7)	-5.7 (± 2.0)	0.0 (± 2.7)

Statistical analyses

Statistical analysis title	Alirocumab:T2DM Subjects vs. Placebo:T2DM Subjects

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant in relevant diabetes stratum). Multiple imputation approach followed by robust regression model.

Comparison groups	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects v Placebo Q2W: T2DM Subjects

Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0902 [29]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	0.9

Notes:

[29] - Threshold for significance at 0.05 level.

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

End point title	Percent Change From Baseline in LDL-C Particle Number at Week 24 - 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 4 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 value 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	22	272	134
Units: percent change				
least squares mean (standard error)	-44.4 (± 3.2)	-4.4 (± 4.6)	-38.3 (± 1.3)	1.9 (± 1.9)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

LDL-C particle size was calculated from lipid subfractions by NMR spectroscopy. Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline data from Week 4 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 size value on- or off-treatment (LDL-C particle size 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: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	22	267	134
Units: percent change				
least squares mean (standard error)	-2.3 (± 0.3)	0.8 (± 0.5)	-2.8 (± 0.1)	-0.3 (± 0.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Weeks 12 and 24 - ITT Analysis

End point title	Absolute Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Weeks 12 and 24 - ITT Analysis

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: percentage of hemoglobin				
arithmetic mean (standard deviation)				
Change at Week 12 (n=48, 22, 281, 138)	0.00 (± 0.46)	-0.22 (± 0.39)	-0.04 (± 0.57)	0.00 (± 0.58)
Change at Week 24 (n=47, 22, 261, 135)	-0.03 (± 0.60)	-0.23 (± 0.36)	0.18 (± 0.74)	0.06 (± 0.66)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in HbA1c at Weeks 12 and 24 - On-Treatment Analysis

End point title	Absolute Change From Baseline in HbA1c at Weeks 12 and 24 - On-Treatment Analysis

End point description:

Absolute change = HbA1c value at specified weeks minus HbA1c value at baseline. mITT population. Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: percentage of hemoglobin				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 48, 22, 275, 136)	0.00 (± 0.46)	-0.22 (± 0.39)	-0.04 (± 0.57)	0.00 (± 0.59)
Change at Week 24 (n= 43, 20, 243, 129)	-0.05 (± 0.61)	-0.27 (± 0.34)	0.18 (± 0.74)	0.06 (± 0.67)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: mmol/L				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 46, 20, 278, 138)	0.23 (± 4.44)	0.45 (± 4.73)	0.25 (± 2.73)	0.13 (± 2.73)
Change at Week 24 (n= 46, 22, 257, 135)	0.52 (± 5.20)	0.81 (± 4.21)	0.52 (± 3.43)	0.55 (± 2.62)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in FPG at Weeks 12 and 24 - On-Treatment Analysis

End point title	Absolute Change From Baseline in FPG at Weeks 12 and 24 - On-Treatment Analysis

End point description:

Absolute change = FPG value at specified weeks minus FPG value at baseline. mITT population. Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: mmol/L				
arithmetic mean (standard deviation)				
Change at Week 12 (n=46, 20, 272, 136)	0.23 (± 4.44)	0.45 (± 4.73)	0.22 (± 2.70)	0.15 (± 2.74)
Change at Week 24 (n= 42, 20, 240, 129)	0.38 (± 5.24)	0.71 (± 4.19)	0.52 (± 3.47)	0.48 (± 2.53)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total Daily Insulin Dose at Weeks 12 and 24 - ITT Analysis

End point title	Absolute Change From Baseline in Total Daily Insulin Dose at

	Weeks 12 and 24 - ITT Analysis

End point description:

Absolute change = total daily insulin dose at specified weeks minus baseline value. ITT population . Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: units (U)				
arithmetic mean (standard deviation)				
Change at Week 12 (n=47, 21, 279, 136)	-10.0 (± 48.7)	-1.3 (± 9.6)	0.2 (± 7.9)	1.4 (± 11.4)
Change at Week 24 (n= 48, 23, 258, 130)	-2.2 (± 11.3)	-0.8 (± 9.8)	2.2 (± 14.8)	1.6 (± 11.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Total Daily Insulin Dose at Weeks 12 and 24 - On-Treatment Analysis

End point title	Absolute Change From Baseline in Total Daily Insulin Dose at Weeks 12 and 24 - On-Treatment Analysis

End point description:

Absolute change = total daily insulin dose at specified weeks minus baseline value. mITT population. Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: units (U)				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 47, 21, 278, 135)	-10.0 (± 48.7)	-1.3 (± 9.6)	0.2 (± 7.9)	1.4 (± 11.4)
Change at Week 24 (n=48, 23, 257, 129)	-2.2 (± 11.3)	-0.8 (± 9.8)	1.7 (± 11.7)	1.6 (± 11.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Insulin Daily Dose/Kg at Weeks 12 and 24 - ITT Analysis

End point title	Absolute Change From Baseline in Insulin Daily Dose/Kg at Weeks 12 and 24 - ITT Analysis

End point description:

Absolute change = daily insulin dose/kg at specified weeks minus baseline value. ITT population . Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: U/kg				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 47, 21, 279, 136)	-0.1 (± 0.5)	0.0 (± 0.1)	0.0 (± 0.1)	0.0 (± 0.1)
Change at Week 24 (n= 48, 23, 258, 130)	0.0 (± 0.1)	0.0 (± 0.1)	0.0 (± 0.2)	0.0 (± 0.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Insulin Daily Dose/Kg at Weeks 12 and 24 - On-Treatment Analysis

End point title	Absolute Change From Baseline in Insulin Daily Dose/Kg at Weeks 12 and 24 - On-Treatment Analysis

End point description:

Absolute change = daily insulin dose/kg at specified weeks minus baseline value. mITT population. Here, 'n' = subjects with available data at the specified time points for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: U/kg				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 47, 21, 278, 135)	-0.1 (± 0.5)	0.0 (± 0.1)	0.0 (± 0.1)	0.0 (± 0.1)
Change at Week 24 (n= 48, 23, 257, 129)	0.0 (± 0.1)	0.0 (± 0.1)	0.0 (± 0.1)	0.0 (± 0.1)

Statistical analyses

No statistical analyses for this end point

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

End point title	Absolute Change From Baseline in Number of Glucose-Lowering Treatments at Weeks 12 and 24 - 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 weeks minus baseline value. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	25	287	142
Units: glucose lowering treatments				
arithmetic mean (standard deviation)				
Change at week 12	0 (± 0)	0 (± 0)	0 (± 0.1)	0 (± 0.2)
Change at Week 24	0 (± 0)	0 (± 0)	0 (± 0.3)	0 (± 0.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Number of Glucose-Lowering Treatments at Weeks 12 and 24 - On-Treatment Analysis

End point title	Absolute Change From Baseline in Number of Glucose-Lowering Treatments at Weeks 12 and 24 - On-Treatment 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 weeks minus baseline value. mITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T1DM Subjects	Placebo Q2W: T1DM Subjects	Alirocumab 75 mg Q2W/Up to 150 mg Q2W: T2DM Subjects	Placebo Q2W: T2DM Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49	24	284	140
Units: glucose lowering treatments				
arithmetic mean (standard deviation)				
Change at Week 12	0 (± 0)	0 (± 00)	0 (± 0.1)	0 (± 0.2)
Change at Week 24	0 (± 0)	0 (± 0)	0 (± 0.3)	0 (± 0.2)

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 final visit (Week 32) in the study regardless of seriousness or relationship to study drugs.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that is 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	19.1

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 stable, maximally tolerated dose of statin therapy with or without other LMT for 24 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥70 mg/dL (1.81 mmol/L) at Week 8.

Reporting group title	Placebo Q2W

Reporting group description:

Placebo (for alirocumab) SC injection Q2W added to stable, maximally tolerated dose of statin therapy with or without other LMT for 24 weeks.

Serious adverse events	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Placebo Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 344 (9.01%)	16 / 170 (9.41%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Pancreas			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's Disease			

subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Cancer Metastatic			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (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			
Influenza Like Illness			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Hypotension			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			

subjects affected / exposed	1 / 344 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Occlusion			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cardiomyopathy			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid Arteriosclerosis			

subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudoradicular Syndrome			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular Syndrome			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (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	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous Haemorrhage			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Haemorrhage			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (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			
Intervertebral Disc Protrusion			

subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed Connective Tissue Disease			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral Foraminal Stenosis			
subjects affected / exposed	2 / 344 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter Gastroenteritis			

subjects affected / exposed	0 / 344 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot Infection			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (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 / 344 (0.29%)	0 / 170 (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	1 / 344 (0.29%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 344 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 344 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alirocumab 75 mg Q2W/Up to 150 mg Q2W	Placebo Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 344 (4.94%)	9 / 170 (5.29%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 344 (4.94%)	9 / 170 (5.29%)	
occurrences (all)	18	9	

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