Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients With Homozygous Familial Hypercholesterolemia

Summary

EudraCT number	2017-000351-95
Trial protocol	FR AT GR IT
Global end of trial date	13 February 2020

Results information

Result version number	v1 (current)
This version publication date	26 February 2021
First version publication date	26 February 2021

Trial information

Trial identification

Sponsor protocol code	R727-CL-1628

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03156621
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) with alirocumab subcutaneous (SC) every 2 weeks (Q2W) in comparison to placebo after 12 weeks of treatment.

The secondary objectives of the study were:

To evaluate the effect of alirocumab Q2W on other lipid parameters (ie, apolipoprotein [Apo] A-1 and B, non-high-density lipoprotein cholesterol [non-HDL-C], total-cholesterol [TC], proportion of subjects with 15%, 30%, and 50% LDL-C reductions, Lp(a), HDL-C, triglycerides [TG]) in subjects with HoFH
To evaluate the safety and tolerability of alirocumab SC Q2W in subjects with HoFH
To assess the pharmacokinetics of alirocumab SC Q2W in subjects with HoFH
To assess the potential development of anti-drug (alirocumab) antibodies (ADA)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2017
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: 3
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 6

Worldwide total number of subjects	69
EEA total number of subjects	25

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)	61
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 27 centers in 13 countries around Europe, Asia, South Africa, and North America. A total of 85 subjects were screened. Of those,16 were considered screen failures (mainly due to violations of inclusion/exclusion criteria).

Pre-assignment

Screening details:

Sixty-nine of the 85 subjects were eligible and randomized in a 2:1 ratio to receive either alirocumab 150 mg SC Q2W or matching placebo. Randomization was stratified by apheresis treatment status (Yes/No).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo in DBTP

Arm description:

Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period.

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

Dosage and administration details:

Matching placebo SC Q2W

Arm title	Alirocumab 150 mg SC Q2W in DBTP

Arm description:

Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	
Other name	PRALUENT® REGN727 SAR236553
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Alirocumab SC Q2W

Number of subjects in period 1	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP
Started	24	45
Completed	24	45

Period 2

Period 2 title	Open-Label Treatment Period (OLTP)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo in DBTP

Arm description:

Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W

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

Dosage and administration details:

Matching placebo SC Q2W
**Not administered in OLTP, only administered in DBTP

Arm title	Alirocumab 150 mg SC Q2W

Arm description:

Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	
Other name	PRALUENT® REGN727 SAR236553
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

150 mg SC Q2W

Number of subjects in period 2	Placebo in DBTP	Alirocumab 150 mg SC Q2W
Started	24	45
Completed	24	42
Not completed	0	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo in DBTP
Reporting group description:	
Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period.	
Reporting group title	Alirocumab 150 mg SC Q2W in DBTP
Reporting group description:	
Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.	

Reporting group values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP	Total
Number of subjects	24	45	69
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	41	61
From 65-84 years	4	4	8
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	45.4	42.3	
standard deviation	± 15.80	± 14.13	-
Sex: Female, Male Units: Participants			
Female	11	24	35
Male	13	21	34
Race/Ethnicity, Customized Units: Subjects			
White	18	36	54
Black or African American	0	2	2
Asian	5	7	12
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	24	43	67
Unknown or Not Reported	0	0	0

Low-density lipoprotein cholesterol (LDL-C)			
Units: milligram/deciLiter (mg/dL)			
arithmetic mean	259.6	295.0	
standard deviation	± 175.75	± 154.59	-
Non-high-density lipoprotein cholesterol (Non-HDL-C)			
Units: mg/dL			
arithmetic mean	282.0	320.5	
standard deviation	± 177.41	± 160.36	-
Total-cholesterol (Total-C)			
Units: mg/dL			
arithmetic mean	325.1	364.3	
standard deviation	± 171.57	± 157.30	-
High-density lipoprotein cholesterol (HDL-C)			
Units: mg/dL			
arithmetic mean	43.2	43.8	
standard deviation	± 11.96	± 14.78	-
Fasting triglycerides (TG)			
Units: mg/dL			
arithmetic mean	111.7	128.0	
standard deviation	± 77.97	± 74.34	-
Lipoprotein(a) [Lp(a)]			
Units: mg/dL			
arithmetic mean	40.0	42.9	
standard deviation	± 36.41	± 36.34	-
Apolipoprotein-B (Apo-B)			
Units: mg/dL			
arithmetic mean	175.0	193.3	
standard deviation	± 95.12	± 87.59	-
Apolipoprotein-A1 (Apo-A1)			
Units: mg/dL			
arithmetic mean	124.8	125.6	
standard deviation	± 24.59	± 28.57	-
Apo-B/Apo-A1			
Units: ratio			
arithmetic mean	1.590	1.635	
standard deviation	± 1.4746	± 0.8693	-

End points

End points reporting groups

Reporting group title	Placebo in DBTP
Reporting group description:	
Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period.	
Reporting group title	Alirocumab 150 mg SC Q2W in DBTP
Reporting group description:	
Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.	
Reporting group title	Placebo in DBTP
Reporting group description:	
Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W	
Reporting group title	Alirocumab 150 mg SC Q2W
Reporting group description:	
Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W	
Subject analysis set title	Alirocumab 150 mg SC Q2W in OLTP
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received at least 1 dose or part of a dose of open-label investigational study drug alirocumab in OLTP	

Primary: Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 (Intent-to-Treat [ITT] estimand)

End point title	Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 (Intent-to-Treat [ITT] estimand)
End point description:	
The percent change in LDL-C from baseline to week 12 is defined as: 100x (LDL-C value at week 12 - LDL-C value at baseline) / LDL-C value at baseline.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.6 (± 6.3)	-26.9 (± 4.6)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	MMRM
Parameter estimate	Least squares (LS) mean difference
Point estimate	-35.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.2
upper limit	-19.9
Variability estimate	Standard error of the mean
Dispersion value	7.8

Notes:

[1] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis

Secondary: Percent change in apolipoprotein (Apo) B from baseline to week 12 (ITT estimand)

End point title	Percent change in apolipoprotein (Apo) B from baseline to week 12 (ITT estimand)

End point description:

ITT estimand; The percent change in Apo B from baseline to week 12 is defined as: 100x (Apo B value at week 12 - Apo B value at baseline) / Apo B value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	7.2 (± 5.0)	-22.5 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	Least squares (LS) mean difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.3
upper limit	-17.3
Variability estimate	Standard error of the mean
Dispersion value	6.3

Notes:

[2] - p-value taken from MMRM (mixed-effect model with repeated measures) analysis

Secondary: Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to week 12

End point title	Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to week 12

End point description:

ITT estimand; The percent change in non-HDL-C from baseline to week 12 is defined as: 100x (non-HDL-C value at week 12 - non-HDL-C value at baseline) / non-HDL-C value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.0 (± 5.9)	-24.8 (± 4.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	MMRM
Parameter estimate	Least squares (LS) mean difference
Point estimate	-32.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.6
upper limit	-18.2
Variability estimate	Standard error of the mean
Dispersion value	7.4

Notes:

[3] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis

Secondary: Percent change in total cholesterol (TC) from baseline to week 12

End point title	Percent change in total cholesterol (TC) from baseline to week 12

End point description:

ITT estimand; The percent change in TC from baseline to week 12 is defined as: 100x (TC value at week 12 - TC value at baseline) / TC value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	6.6 (± 5.0)	-19.8 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	MMRM
Parameter estimate	Least squares (LS) mean difference
Point estimate	-26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.9
upper limit	-14
Variability estimate	Standard error of the mean
Dispersion value	6.2

Notes:
[4] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis.

Secondary: Proportion of subjects with ≥15% reduction in LDL-C at week 12	
End point title	Proportion of subjects with ≥15% reduction in LDL-C at week 12
End point description: ITT estimand	
End point type	Secondary
End point timeframe: At Week 12	

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
number (not applicable)	12.5	61.9		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	48.8

Secondary: Proportion of subjects with ≥30% reduction in LDL-C at week 12	
End point title	Proportion of subjects with ≥30% reduction in LDL-C at week 12
End point description: ITT estimand	
End point type	Secondary

End point timeframe:

At Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
number (not applicable)	4.2	57.1		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	36.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	308.9

Secondary: Percent change in lipoprotein(a) [Lp(a)] from baseline to week 12

End point title	Percent change in lipoprotein(a) [Lp(a)] from baseline to week 12

End point description:

ITT estimand; The percent change in Lp(a) from baseline to week 12 is defined as: 100x (Lp(a) value at week 12 - Lp(a) value at baseline) / Lp(a) value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.8 (± 5.4)	-19.6 (± 4.0)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression model
Parameter estimate	Mean difference (final values)
Point estimate	-28.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.5
upper limit	-15.2
Variability estimate	Standard error of the mean
Dispersion value	6.7

Secondary: Proportion of subjects with ≥50% reduction in LDL-C at week 12

End point title	Proportion of subjects with ≥50% reduction in LDL-C at week 12
End point description: ITT estimand	
End point type	Secondary
End point timeframe: At Week 12	

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
number (not applicable)	0	26.7		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Exact Conditional Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	99999

Secondary: Percent change in HDL-C from baseline to week 12 - ITT analysis

End point title	Percent change in HDL-C from baseline to week 12 - ITT analysis
End point description:	
ITT estimand; The percent change in HDL-C from baseline to week 12 is defined as: 100x (HDL-C value at week 12 - HDL-C value at baseline) / HDL-C value at baseline.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	2.7 (± 3.1)	6.3 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3541 [5]
Method	MMRM
Parameter estimate	Least squares (LS) mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	11.3
Variability estimate	Standard error of the mean
Dispersion value	3.8

Notes:

[5] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis.

Secondary: Percent change in fasting triglycerides (TG) from baseline to week 12

End point title	Percent change in fasting triglycerides (TG) from baseline to week 12

End point description:

ITT estimand; The percent change in TG from baseline to week 12 is defined as: 100x (TG value at week 12 - TG value at baseline) / TG value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	3.9 (± 5.7)	-7.4 (± 4.2)		

Statistical analyses

Statistical analysis title	Alirocumab 150 SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.2
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	7.1

Secondary: Percent change in Apo A-1 from baseline to week 12 -- ITT analysis

End point title	Percent change in Apo A-1 from baseline to week 12 -- ITT analysis

End point description:

ITT estimand; The percent change in Apo A-1 from baseline to week 12 is defined as: 100x (Apo A-1 value at week 12 - Apo A-1 value at baseline) / Apo A-1 value at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	1.4 (± 2.9)	5.0 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	10.7

Variability estimate	Standard error of the mean
Dispersion value	3.6

Secondary: Percent change in LDL-C from baseline to week 12 (on-treatment estimand)

End point title	Percent change in LDL-C from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for LDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.6 (± 6.3)	-26.9 (± 4.6)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	-35.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.2
upper limit	-19.9
Variability estimate	Standard error of the mean
Dispersion value	7.8

Secondary: Percent change in Apo B from baseline to week 12 (on-treatment estimand)

End point title	Percent change in Apo B from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for Apo B from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label nvestigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	7.2 (± 5.0)	-22.5 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.3
upper limit	-17.3
Variability estimate	Standard error of the mean
Dispersion value	6.3

Secondary: Percent change in non-HDL-C from baseline to week 12 (on-treatment estimand)

End point title	Percent change in non-HDL-C from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for non-HDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.0 (± 5.9)	-24.8 (± 4.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	-32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.6
upper limit	-18.2
Variability estimate	Standard error of the mean
Dispersion value	7.4

Secondary: Percent change in TC from baseline to week 12 (on-treatment estimand)

End point title	Percent change in TC from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for TC from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	6.6 (± 5.0)	-19.8 (± 3.7)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SQ Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	-26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.9
upper limit	-14
Variability estimate	Standard error of the mean
Dispersion value	6.2

Secondary: Percent change in Lp(a) from baseline to week 12 (on-treatment estimand)

End point title	Percent change in Lp(a) from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for LP(a) from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	8.8 (± 5.4)	-19.6 (± 4.0)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-28.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.5
upper limit	-15.2
Variability estimate	Standard error of the mean
Dispersion value	6.7

Secondary: Percent change in HDL-C from baseline to week 12 - (on-treatment estimand)

End point title	Percent change in HDL-C from baseline to week 12 - (on-treatment estimand)

End point description:

Percent change for HDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	2.7 (± 3.1)	6.3 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	11.3
Variability estimate	Standard error of the mean
Dispersion value	3.8

Secondary: Percent change in fasting TG from baseline to week 12 (on-treatment estimand)

End point title	Percent change in fasting TG from baseline to week 12 (on-treatment estimand)

End point description:

Percent change for fasting TG from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	3.9 (± 5.7)	-7.4 (± 4.2)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.2
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	7.1

Secondary: Percent change in Apo A-1 from baseline to week 12 -- (on-treatment estimand)

End point title	Percent change in Apo A-1 from baseline to week 12 -- (on-treatment estimand)

End point description:

Percent change for Apo A-1 from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	1.4 (± 2.9)	5.0 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	3.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	10.7
Variability estimate	Standard error of the mean
Dispersion value	3.6

Secondary: Proportion of subjects with ≥15% reduction, ≥30% reduction, and ≥50% reduction in LDL-C at week 12 (on-treatment estimand)

End point title	Proportion of subjects with ≥15% reduction, ≥30% reduction, and ≥50% reduction in LDL-C at week 12 (on-treatment estimand)

End point description:

End point type	Secondary

End point timeframe:

At Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
number (not applicable)				
≥ 15%	12.5	61.9		
≥ 30%	4.2	57.1		
≥ 50%	0	26.7		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W

Statistical analysis description:

≥ 15% reduction

Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	12.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	48.8

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Statistical analysis description: ≥ 30% reduction	
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	36.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	308.9

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Statistical analysis description: ≥ 50% reduction	
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	99999

Secondary: Absolute change in the ratio of Apo B/Apo A-1 from baseline to week 12 (ITT estimand)

End point title	Absolute change in the ratio of Apo B/Apo A-1 from baseline to week 12 (ITT estimand)
End point description: ITT estimand	
End point type	Secondary

End point timeframe:
Baseline to Week 12

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45		
Units: Percentage				
least squares mean (standard error)	0.0 (± 0.1)	-0.3 (± 0.1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W
Comparison groups	Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares (LS) mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Incidence of anti-drug antibodies (ADA) to REGN727 over time

End point title	Incidence of anti-drug antibodies (ADA) to REGN727 over

End point description:

End point type	Secondary

End point timeframe:
26 weeks

Notes:
[6] - 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: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	44		
Units: Subjects				
Treatment-Emergent	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events (AEs)

End point title	Incidence of Adverse Events (AEs)

End point description:

All AEs will be recorded from time of informed consent to end of study. Only treatment-emergent adverse events (TEAE) will be reported. Double-blind TEAE observation period is defined as time from first dose of double-blind study drug to last dose of double-blind study drug +70 days, or up to day before first dose of open-label study drug administration, whichever is earlier. Open-label TEAE observation period is defined as time from first open-label study treatment administration to last open-label study treatment administration +70 days.

End point type	Secondary

End point timeframe:

Baseline to week 32 (End of Study)

End point values	Placebo in DBTP	Alirocumab 150 mg SC Q2W in DBTP	Alirocumab 150 mg SC Q2W in OLTP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	24	45	69	
Units: Subjects				
Subjects with any TEAE	12	20	24	
Subjects with TEAE Serious Adverse Event (SAE)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 1) to end of study (Day 225)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP

Reporting group description:

Participants received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all participants received open-label alirocumab SC Q2W

Reporting group title	Alirocumab 150 Q2W in DBTP and OLTP

Reporting group description:

Participants in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all participants received open-label alirocumab SC Q2W

Serious adverse events	Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP	Alirocumab 150 Q2W in DBTP and OLTP	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 45 (2.22%)	
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	Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP	Alirocumab 150 Q2W in DBTP and OLTP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)	14 / 45 (31.11%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 10	 3 / 45 (6.67%) 3	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 0 / 24 (0.00%) 0	 4 / 45 (8.89%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 2 0 / 24 (0.00%) 0	 0 / 45 (0.00%) 0 3 / 45 (6.67%) 3	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1 2 / 24 (8.33%) 3	 5 / 45 (11.11%) 7 2 / 45 (4.44%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2017	Refining diagnostic criteria; adding additional assessments; sample size adjustment in statistical methods; correct inconsistencies and make additional editorial changes
11 July 2017	Added exclusion criteria; extended treatment emergent AE period; clarified text and added definitions; added an assessment for hepatitis C and process instructions; edits and clarifications.
04 January 2019	Increased sample size; revised ITT population definition

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported