Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia Undergoing Lipid Apheresis Therapy

Summary

EudraCT number	2014-001917-20
Trial protocol	DE
Global end of trial date	20 April 2016

Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018

Trial information

Trial identification

Sponsor protocol code	R727-CL-1216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02326220
WHO universal trial number (UTN)	-
Other trial identifiers	Study name: ODYSSEY ESCAPE

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States,
Public contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials information, 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	31 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2016
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 evaluate the effect of alirocumab 150 mg every 2 weeks (Q2W) in comparison with placebo on the frequency of low-density lipoprotein (LDL) apheresis treatments in subjects with heterozygous familial hypercholesterolemia (HeFH) undergoing weekly or bi-weekly LDL apheresis therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Subjects undergoing LDL apheresis therapy every 1 or 2 weeks were enrolled in this study while maintaining background lipid modifying therapy (LMT) treatment throughout the study. All patients were being treated with the maximally tolerated clinically-relevant LMT.

Evidence for comparator: -

Actual start date of recruitment	09 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	62
EEA total number of subjects	30

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)	41
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Germany and the United States between 09 Mar 2015 and 20 Apr 2016. A total of 76 subjects were screened, of which 62 were enrolled and randomized in the study.

Pre-assignment

Screening details:

Randomization was stratified according to the frequency of the apheresis procedure (every 7 or 14 days) and Lipoprotein (a) (Lp [a]) levels (normal or elevated). Assignment to treatment arms was done using an Interactive Voice/Web Response System in 1:2 ratio to placebo or alirocumab 150 mg Q2W.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Placebo (for alirocumab) subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
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	Alirocumab 150 mg Q2W

Arm description:

Alirocumab 150 mg subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	Praluent®
Pharmaceutical forms	Solution for injection in pre-filled syringe
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	Placebo Q2W	Alirocumab 150 mg Q2W
Started	21	41
Completed	20	37
Not completed	1	4
Consent withdrawn by subject	-	1
Adverse events	1	2
Poor compliance to protocol	-	1

Period 2

Period 2 title	Open-label Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Alirocumab 150 mg Q2W

Arm description:

Alirocumab 150 mg SC injection Q2W starting from Week 18 up to Week 76 or until alirocumab became commercially available in the subject's country, whichever occurred first. Apheresis treatment was not required in the open-label treatment period and could be stopped or continued at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	Praluent®
Pharmaceutical forms	Solution for injection in pre-filled syringe
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 2[1]	Alirocumab 150 mg Q2W
Started	29
Completed	27
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Entry into the open-label treatment period was available only to patients who were study participants in a country in which alirocumab was not commercially available.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.	

Reporting group values	Placebo Q2W	Alirocumab 150 mg Q2W	Total
Number of subjects	21	41	62
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	57	59.5	
standard deviation	± 10.5	± 9.2	-
Gender categorical			
Units: Subjects			
Female	11	15	26
Male	10	26	36
Race			
Units: Subjects			
White	21	39	60
Black or African American	0	2	2
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	21	41	62
Frequency in which Subjects are Undergoing Apheresis			
Units: Subjects			
Every week	9	18	27
Every 2 weeks	12	23	35
Lipoprotein (a) in mg/dL			
Units: mg/dL			
arithmetic mean	45.7	43	
standard deviation	± 49.5	± 54.5	-
Lipoprotein (a) in g/L			
Units: g/L			
arithmetic mean	0.457	0.43	

standard deviation	± 0.495	± 0.545	-
Calculated LDL-C in mg/dL			
Calculated LDL-C from Friedewald formula (LDL-C = Total cholesterol [Total-C] - High-Density Lipoprotein Cholesterol [HDL-C] - [Triglyceride/5]).			
Units: mg/dL			
arithmetic mean	191.6	175.1	
standard deviation	± 68.9	± 54.6	-
Calculated LDL-C in mmol/L			
Units: mmol/L			
arithmetic mean	4.964	4.534	
standard deviation	± 1.783	± 1.413	-

End points

End points reporting groups

Reporting group title	Placebo Q2W
Reporting group description:	
Placebo (for alirocumab) subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg subcutaneous (SC) injection Q2W up to Week 16. Apheresis frequency was fixed (weekly or bi-weekly) until Week 6, then it was adjusted according to the response to treatment.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Alirocumab 150 mg SC injection Q2W starting from Week 18 up to Week 76 or until alirocumab became commercially available in the subject's country, whichever occurred first. Apheresis treatment was not required in the open-label treatment period and could be stopped or continued at the investigator's discretion.	

Primary: Rate of Apheresis Treatment From Week 7 to Week 18

End point title	Rate of Apheresis Treatment From Week 7 to Week 18
End point description:	
The normalized rate of apheresis was defined for each subject as the number of actual apheresis treatments received from week 7 to week 18 divided by the number of planned apheresis treatments per randomization strata at baseline (6 for Q2W and 12 for QW). Intent-to-treat (ITT) population defined as all randomized subjects and were analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe:	
Week 7 up to Week 18 (before the start of open-label treatment dose)	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Rate of treatment				
arithmetic mean (standard deviation)	0.853 (± 0.184)	0.378 (± 0.376)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W
Statistical analysis description:	
Analysis was performed using the ranked analysis of covariance (ANCOVA) model with baseline frequency of the apheresis procedure (QW or Q2W) and Lipoprotein (a) (Lp [a]) levels (normal or elevated) as fixed effect and the baseline LDL-C level as a covariate. Median treatment difference and 95% confidence interval (CI) was derived from the Hodges-Lehmann (H-L) estimation and Moses distribution free CI, respectively.	
Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Ranked Median Difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.333
upper limit	0.75

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Calculated Low-density Lipoprotein Cholesterol (LDL-C) (Pre-Apheresis) to Week 6

End point title	Percent Change From Baseline in Calculated Low-density Lipoprotein Cholesterol (LDL-C) (Pre-Apheresis) to Week 6

End point description:

Adjusted Least-squares (LS) means and standard errors at Week 6 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 2 to Week 18 regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population that included all randomized subjects with baseline and at least one post-baseline pre-apheresis calculated LDL-C value up to week 6, analyzed according to the treatment group allocated by randomization.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	1.6 (± 3.1)	-53.6 (± 2.3)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

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.

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	MMRM
Parameter estimate	Least Square (LS) mean difference
Point estimate	-55.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63
upper limit	-47.5

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Rate of Apheresis Treatment from Week 15 to Week 18

End point title	Rate of Apheresis Treatment from Week 15 to Week 18

End point description:

The normalized rate of apheresis was defined for each subject as the number of actual apheresis treatments received from week 15 to week 18 divided by the planned apheresis treatments per randomization strata at baseline (2 for Q2W and 4 for QW). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 15 up to Week 18 (before the start of open-label treatment dose)

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Rate of treatment				
median (full range (min-max))	1 (0 to 1)	0.500 (0 to 1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [3]
Method	ANCOVA
Parameter estimate	Ranked Median Difference (final values)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.5

Notes:

[3] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Apolipoprotein B (Apo B) (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Apolipoprotein B (Apo B) (Pre-apheresis) to Week 6

End point description:

Adjusted LS means and standard errors at Week 6 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	1.2 (± 3)	-42.8 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.3
upper limit	-36.6

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) (Pre-apheresis) to Week 6

End point description:

Adjusted LS means and standard errors at Week 6 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	2.8 (± 2.9)	-47.1 (± 2.1)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.3
upper limit	-42.7

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Total Cholesterol (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Total Cholesterol (Pre-apheresis) to Week 6

End point description:

Adjusted LS means and standard errors at Week 6 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	3.1 (± 2.5)	-36.4 (± 1.8)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-39.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.6
upper limit	-33.2

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Percent Change From Baseline in Apolipoprotein A (Apo A1) (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Apolipoprotein A (Apo A1) (Pre-apheresis) to Week 6

End point description:

Adjusted LS means and standard errors at Week 6 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	0 (± 3.3)	4.2 (± 2.4)		

Statistical analyses

Statistical analysis title	Alirocumab 150 mg Q2W vs Placebo Q2W

Statistical analysis description:

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

Comparison groups	Alirocumab 150 mg Q2W v Placebo Q2W
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3012 [7]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	12.3

Notes:

[7] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with At least (>=) 30% Reduction in Calculated LDL-C (Pre-apheresis) at Week 6

End point title	Percentage of Subjects with At least (>=) 30% Reduction in Calculated LDL-C (Pre-apheresis) at Week 6

End point description:

Percentage of subjects at Week 6 was obtained from a last observation carried forward (LOCF) model for handling of missing data. All available post-baseline data regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percentage of subjects				
number (not applicable)	4.8	95.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At least (>=) 50% Reduction in Calculated LDL-C (Pre-apheresis) at Week 6

End point title	Percentage of Subjects with At least (>=) 50% Reduction in Calculated LDL-C (Pre-apheresis) at Week 6

End point description:

Percentage of subjects at Week 6 was obtained from LOCF model for handling of missing data. All available post-baseline data regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percentage of subjects				
number (not applicable)	0	63.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Calculated LDL-C (Pre-Apheresis) to Week 18

End point title	Percent Change From Baseline in Calculated LDL-C (Pre-Apheresis) to Week 18

End point description:

Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary
End point timeframe:	
From Baseline to Week 18	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	4 (± 6.2)	-42.3 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein B (Apo B) (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in Apolipoprotein B (Apo B) (Pre-apheresis) to Week 18
End point description:	
Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 18	

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	1.7 (± 4.8)	-33.8 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Non-HDL-C (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in Non-HDL-C (Pre-apheresis) to

	Week 18

End point description:

Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	4.7 (± 5.6)	-35.7 (± 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Cholesterol (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in Total Cholesterol (Pre-apheresis) to Week 18

End point description:

Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	4.7 (± 4.7)	-27.1 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apo A1 (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in Apo A1 (Pre-apheresis) to Week 18

End point description:

Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	-0.7 (± 3.4)	7.8 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At least (>=) 30% Reduction in Calculated LDL-C (Pre-apheresis) at Week 18

End point title	Percentage of Subjects with At least (>=) 30% Reduction in Calculated LDL-C (Pre-apheresis) at Week 18

End point description:

Percentage of subjects at Week 18 was obtained from LOCF model for handling of missing data. All available post-baseline data regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percentage of subjects				
number (not applicable)	0	65.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At least (>=) 50% Reduction in Calculated LDL-C (Pre-apheresis) at Week 18

End point title	Percentage of Subjects with At least (>=) 50% Reduction in Calculated LDL-C (Pre-apheresis) at Week 18

End point description:

Percentage of subjects at Week 18 was obtained from LOCF model for handling of missing data. All available post-baseline data regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percentage of subjects				
number (not applicable)	0	43.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in W-BQ22 (Well-being Questionnaire) Index Score at Week 18

End point title	Change From Baseline in W-BQ22 (Well-being Questionnaire) Index Score at Week 18

End point description:

The W-BQ22 (well-being) questionnaire was a standardized and generic instrument used for measuring the impact of hypercholesterolemia and treatment on well-being of subjects. The general well-being score was calculated as the sum of 22 questions in the W-BQ22 questionnaire (each question scored from 0 to 3 [0 = not at all and 3 = all the time]). Total score for 22 questions range from 0 to 66 [0 = worst condition and 66 = best well-being condition). Analysis was performed on Well-Being analysis set included all randomized and treated subjects with complete baseline and complete post-baseline evaluations of the 22-question well-being questionnaire.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: units on a score				
least squares mean (standard error)	-1.43 (± 1.441)	0.91 (± 1.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lipoprotein (a) (Lp [a]) (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Lipoprotein (a) (Lp [a]) (Pre-apheresis) to Week 6

End point description:

Adjusted means and standard errors at Week 6 from a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	-4 (± 5.1)	-18.1 (± 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) (Pre-apheresis) to Week 6

End point description:

Adjusted LS means and standard errors at Week 6 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis)

regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	4 (± 3.4)	9.3 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Triglyceride (TG) levels (Pre-apheresis) to Week 6

End point title	Percent Change From Baseline in Triglyceride (TG) levels (Pre-apheresis) to Week 6

End point description:

Adjusted means and standard errors at Week 6 from a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 6

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	3 (± 5.6)	-12.9 (± 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lp (a) (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in Lp (a) (Pre-apheresis) to Week 18

End point description:

Adjusted means and standard errors at Week 18 from a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	-1.2 (± 8)	-6.1 (± 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL-C (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in HDL-C (Pre-apheresis) to Week 18

End point description:

Adjusted LS means and standard errors at Week 18 were obtained from MMRM to account for missing data. All available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	2.4 (± 5)	10.9 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in TG Levels (Pre-apheresis) to Week 18

End point title	Percent Change From Baseline in TG Levels (Pre-apheresis) to Week 18

End point description:

Adjusted means and standard errors at Week 18 from a multiple imputation approach followed by robust regression model including all available post-baseline data from Week 2 (pre-apheresis) to Week 18 (pre-apheresis) regardless of status on- or off-treatment were used in the model (ITT analysis). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 18

End point values	Placebo Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	41		
Units: Percent change				
least squares mean (standard error)	4.1 (± 7.9)	-2.4 (± 5.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final study end visit (maximum duration: 46 weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs developed/worsened during 'on treatment period'(double blind treatment-emergent period: time from first dose of study drug to last double-blind dose+70 days, prior to first open-label dose of study drug; open-label treatment emergent period: time from first open-label dose of study drug to last dose+70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo Q2W (DB Period)

Reporting group description:

Placebo (for alirocumab) subcutaneous (SC) injection Q2W up to Week 16 (mean exposure of 17 weeks).

Reporting group title	Alirocumab 150 mg Q2W (DB Period)

Reporting group description:

Alirocumab 150 mg SC injection Q2W up to Week 16 (mean exposure of 17 weeks).

Reporting group title	Alirocumab 150 mg Q2W (OLE Period)

Reporting group description:

Alirocumab 150 mg SC injection Q2W from Week 18 (mean exposure of 17 weeks).

Serious adverse events	Placebo Q2W (DB Period)	Alirocumab 150 mg Q2W (DB Period)	Alirocumab 150 mg Q2W (OLE Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)	4 / 41 (9.76%)	1 / 29 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Muscle rupture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery restenosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 41 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Shunt thrombosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 41 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 21 (0.00%)	2 / 41 (4.88%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 21 (4.76%)	0 / 41 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 41 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 41 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo Q2W (DB Period)	Alirocumab 150 mg Q2W (DB Period)	Alirocumab 150 mg Q2W (OLE Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)	22 / 41 (53.66%)	2 / 29 (6.90%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 21 (9.52%)	0 / 41 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	3 / 41 (7.32%)	0 / 29 (0.00%)
occurrences (all)	2	5	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 41 (2.44%)	2 / 29 (6.90%)
occurrences (all)	0	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 21 (9.52%)	6 / 41 (14.63%)	0 / 29 (0.00%)
occurrences (all)	2	6	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	4 / 41 (9.76%)	0 / 29 (0.00%)
occurrences (all)	0	4	0
Nausea			
subjects affected / exposed	3 / 21 (14.29%)	2 / 41 (4.88%)	0 / 29 (0.00%)
occurrences (all)	4	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)	3 / 41 (7.32%)	0 / 29 (0.00%)
occurrences (all)	2	5	0
Back pain			
subjects affected / exposed	2 / 21 (9.52%)	2 / 41 (4.88%)	0 / 29 (0.00%)
occurrences (all)	4	4	0
Myalgia			
subjects affected / exposed	1 / 21 (4.76%)	5 / 41 (12.20%)	0 / 29 (0.00%)
occurrences (all)	1	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 21 (9.52%)	4 / 41 (9.76%)	1 / 29 (3.45%)
occurrences (all)	2	4	2
Upper respiratory tract infection			
subjects affected / exposed	4 / 21 (19.05%)	3 / 41 (7.32%)	0 / 29 (0.00%)
occurrences (all)	4	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	Following changes were made: - Allowed flexibility in apheresis treatment eligibility requirements; - Added an open-label treatment period; - Updated site locations; - made minor clarifications.
06 July 2015	Following changes were made: - Updated eligibility requirements that were consistent with the known safety profile of the study drug; - Made a minor clarification to the text regarding the apheresis schedule.
22 September 2015	Following changes were made: -Noted that entry into the open-label treatment period was only available to subjects who were study participants in a country in which alirocumab not commercially available (sites in Germany); -Indicated that treatment in the open-label period of the study would continue for a maximum of 76 weeks or until alirocumab was commercially available in the subject's country, whichever comes first (sites in Germany); -Clarified that subjects who chose not to participate in the open-label treatment period, or who were study subjects in a country in which alirocumab was commercially available (sites in the US), would be seen at week 26 for the double-blind treatment period end of study visit. These subjects were considered to have completed the study at this end of study visit;- -Specified that the primary analysis would be performed following the completion of the double-blind treatment period and made minor administrative corrections/clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported