



## Clinical trial results:

### An Open-Label Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents With Homozygous Familial Hypercholesterolemia

#### Summary

EudraCT number	2017-002297-39
Trial protocol	NO FR NL IT DK AT SI ES BG Outside EU/EEA
Global end of trial date	17 February 2020

#### Results information

Result version number	v2 (current)
This version publication date	05 January 2023
First version publication date	28 August 2020
Version creation reason	• Correction of full data set Updated safety optional field

#### Trial information

##### Trial identification

Sponsor protocol code	EFC14660
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03510715
WHO universal trial number (UTN)	U1111-1200-2046

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)	Yes
EMA paediatric investigation plan number(s)	EMA-001169-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 March 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 February 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of alirocumab (75 or 150 milligram [mg] depending on body weight [BW]), administered every 2 weeks (Q2W), on low-density lipoprotein cholesterol (LDL-C) levels at Week 12 of treatment in children with homozygous familial hypercholesterolemia (hoFH) of 8 to 17 years of age on top of background treatments.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	18
EEA total number of subjects	8

Notes:

<b>Subjects enrolled per age group</b>	
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)	8
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 10 active centres (which screened at least 1 subject) in 10 countries worldwide. Overall 20 subjects were screened between 31 August 2018 and 4 January 2019, of whom 2 were screen failures. Of the 10 centers which screened subjects, 9 centers enrolled at least 1 subject.

### Pre-assignment

Screening details:

A total of 18 subjects were enrolled and received treatment in this study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Alirocumab 75 mg Q2W/up to 150 mg Q2W

Arm description:

Subjects with BW less than (<) 50 kilograms (kg) received subcutaneous (SC) injection of alirocumab 75 mg Q2W for 48 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 in case of increase in BW with BW greater than or equal to [ $\geq$ ] 50 kg.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 75 mg alirocumab Q2W for 48 weeks. After Week 12, dose was up-titrated to 150 mg Q2W in case of change in BW with BW  $\geq$  50 kg.

<b>Arm title</b>	Alirocumab 150 mg Q2W
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Arm description:

Subjects with BW  $\geq$  50 kg received SC injection of alirocumab 150 mg Q2W for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 150 mg alirocumab Q2W for 48 weeks.

Number of subjects in period 1	Alirocumab 75 mg Q2W/up to 150 mg Q2W	Alirocumab 150 mg Q2W
Started	9	9
Completed	8	9
Not completed	1	0
Adverse event	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Alirocumab 75 mg Q2W/up to 150 mg Q2W
Reporting group description:	
Subjects with BW less than (<) 50 kilograms (kg) received subcutaneous (SC) injection of alirocumab 75 mg Q2W for 48 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 in case of increase in BW with BW greater than or equal to [ $\geq$ ] 50 kg.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description:	
Subjects with BW $\geq$ 50 kg received SC injection of alirocumab 150 mg Q2W for 48 weeks.	

Reporting group values	Alirocumab 75 mg Q2W/up to 150 mg Q2W	Alirocumab 150 mg Q2W	Total
Number of subjects	9	9	18
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	10.4	14.3	
standard deviation	$\pm 1.5$	$\pm 2.4$	-
Gender categorical			
Units: Subjects			
Female	4	5	9
Male	5	4	9
Race			
Units: Subjects			
White	6	5	11
Black or African American	0	1	1
Asian	1	2	3
American Indian or Alaska Native	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Low-Density Lipoprotein Cholesterol (LDL-C)			
Units: milligrams per decilitre (mg/dL)			
arithmetic mean	437.7	308.3	
standard deviation	$\pm 192.8$	$\pm 181.6$	-

## End points

### End points reporting groups

Reporting group title	Alirocumab 75 mg Q2W/up to 150 mg Q2W
Reporting group description: Subjects with BW less than (<) 50 kilograms (kg) received subcutaneous (SC) injection of alirocumab 75 mg Q2W for 48 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 in case of increase in BW with BW greater than or equal to [ $\geq$ ] 50 kg.	
Reporting group title	Alirocumab 150 mg Q2W
Reporting group description: Subjects with BW $\geq$ 50 kg received SC injection of alirocumab 150 mg Q2W for 48 weeks.	
Subject analysis set title	Alirocumab
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received either 75 mg (BW < 50 kg) or 150 mg (BW $\geq$ 50 kg) alirocumab subcutaneously Q2W for 48 weeks.	

### Primary: Percent Change From Baseline in Low-Density Lipoprotein Cholesterol (LDL-C) at Week 12: Intent-to-Treat (ITT) Analysis

End point title	Percent Change From Baseline in Low-Density Lipoprotein Cholesterol (LDL-C) at Week 12: Intent-to-Treat (ITT) Analysis <sup>[1]</sup>
End point description: Adjusted least square (LS) means and standard errors were obtained from the mixed model analysis with repeated measures (MMRM) to account for missing data using all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population which included all enrolled subjects who received at least one dose or partial dose of alirocumab.	
End point type	Primary
End point timeframe: Baseline to Week 12	
Notes: [1] - 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: Only descriptive analysis was planned to be reported.	

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent change				
least squares mean (standard error)	-4.1 ( $\pm$ 9.0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Low-Density Lipoprotein Cholesterol at Week 12: On-treatment Analysis

End point title	Percent Change From Baseline in Low-Density Lipoprotein Cholesterol at Week 12: On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline on-treatment data from Week 4 to Week 48 (on-treatment analysis). As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)	-4.1 (± 9.0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Low-Density Lipoprotein Cholesterol at Weeks 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Low-Density Lipoprotein Cholesterol at Weeks 24 and 48: ITT Analysis/On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 24 and 48

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 24	-10.1 (± 7.6)			
Week 48	4.2 (± 12.8)			



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Apolipoprotein (Apo) B at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Apolipoprotein (Apo) B at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 12, 24 and 48

<b>End point values</b>	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 12	-4.2 (± 6.8)			
Week 24	-11.8 (± 6.1)			
Week 48	0.9 (± 10.4)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 12, 24 and 48 - ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 12, 24 and 48 - ITT Analysis/On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing

data using all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
End point timeframe:	
Baseline to Weeks 12, 24 and 48	

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 12	-3.9 (± 8.3)			
Week 24	-9.2 (± 7.3)			
Week 48	5.7 (± 13.1)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Total Cholesterol (Total-C) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Weeks 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
End point timeframe:	
Baseline to Weeks 12, 24 and 48	

<b>End point values</b>	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 12	-1.9 (± 7.2)			
Week 24	-6.3 (± 6.5)			
Week 48	5.5 (± 10.7)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Lipoprotein a (Lp) (a) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Lipoprotein a (Lp) (a) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
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End point description:

Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data from Week 4 to Week 48 regardless of status on-or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 12, 24 and 48

<b>End point values</b>	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
arithmetic mean (standard error)				
Week 12	7.4 (± 7.6)			
Week 24	-5.2 (± 8.1)			
Week 48	-6.4 (± 12.2)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in High Density Lipoprotein Cholesterol (HDL-C) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in High Density Lipoprotein Cholesterol (HDL-C) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
End point description:	
Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Weeks 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
Baseline to Weeks 12, 24 and 48	

<b>End point values</b>	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 12	13.0 (± 5.9)			
Week 24	8.9 (± 4.4)			
Week 48	10.1 (± 5.5)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Fasting Triglycerides (TG) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Fasting Triglycerides (TG) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
End point description:	
Adjusted means and standard errors were obtained from a multiple imputation approach followed by a robust regression model including all available post-baseline data from Week 4 to Week 48 regardless of status on-or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
Baseline to Weeks 12, 24 and 48	

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
arithmetic mean (standard error)				
Week 12	2.8 (± 8.0)			
Week 24	5.2 (± 16.2)			
Week 48	10.0 (± 8.2)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Apolipoprotein A1 (Apo A1) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percent Change From Baseline in Apolipoprotein A1 (Apo A1) at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
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End point description:

Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Week 4 to 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data was planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Weeks 12, 24 and 48

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percent Change				
least squares mean (standard error)				
Week 12	11.3 (± 6.9)			
Week 24	14.6 (± 6.0)			
Week 48	11.3 (± 5.8)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting ≥15 Percent (%) Reduction in LDL-C Level at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Percentage of Subjects Reporting $\geq 15$ Percent (%) Reduction in LDL-C Level at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
End point description:	
Adjusted Percentage were obtained from a multiple imputation approach for handling of missing data including all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
Weeks 12, 24 and 48	

<b>End point values</b>	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of subjects				
number (confidence interval 95%)				
Week 12	50.0 (26.2 to 73.8)			
Week 24	50.0 (26.2 to 73.8)			
Week 48	39.0 (15.8 to 62.2)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Baseline in LDL-C Level at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis

End point title	Absolute Change From Baseline in LDL-C Level at Weeks 12, 24 and 48: ITT Analysis/On-treatment Analysis
End point description:	
Adjusted LS means and standard errors were obtained from the MMRM model to account for missing data using all available post-baseline data from Week 4 to Week 48 regardless of status on- or off-treatment used in the model (ITT analysis). Although separate analyses of all available data (ITT analysis) and only data collected within a defined time window (On-treatment analysis) were planned, if all values used in the ITT approach were within the on-treatment time window, the on-treatment analysis would be identical to the ITT analysis, the results would be identical and a single endpoint presenting the results for both types of analysis would be provided. As pre-specified, efficacy analysis data were planned to be collected and analysed for all doses combined (i.e. for combined population). Analysis was performed on ITT population.	
End point type	Secondary
End point timeframe:	
Baseline to Weeks 12, 24 and 48	

End point values	Alirocumab			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: mg/dL				
least squares mean (standard error)				
Week 12	-33.4 (± 19.1)			
Week 24	-43.0 (± 19.0)			
Week 48	-15.0 (± 25.7)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Tanner Staging at Weeks 12, 24 and 48

End point title	Number of Subjects With Tanner Staging at Weeks 12, 24 and 48
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End point description:

Tanner stage defines physical measurements of development in children and adolescent based on external primary and secondary sex characteristics. Subjects were evaluated for pubic hair distribution, breast development (only females) and genital development (only males), and classified in 3 categories as: Prepubescent (defined as a person just before start of the development of adult sexual characteristics), Pubescent (defined as a person at or approaching the age of puberty), Postpubescent (sexually mature or a person who has completed puberty). Analysis was performed on safety population which included subjects who received at least one dose or partial dose of alirocumab. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24 and 48

End point values	Alirocumab 75 mg Q2W/up to 150 mg Q2W	Alirocumab 150 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
number (not applicable)				
Baseline: Prepubescent (n = 9, 9)	3	0		
Baseline: Pubescent (n = 9, 9)	6	9		
Baseline: Post-pubescent (n = 9, 9)	0	0		
Week 12: Prepubescent (n = 9, 9)	3	0		
Week 12: Pubescent (n = 9, 9)	6	8		
Week 12: Post-pubescent (n=9, 9)	0	1		
Week 24: Prepubescent (n = 8, 9)	2	0		
Week 24: Pubescent (n = 8, 9)	6	8		
Week 24: Post-pubescent (n = 8, 9)	0	1		

Week 48: Prepubescent (n = 8, 9)	1	0		
Week 48: Pubescent (n = 8, 9)	7	7		
Week 48: Post-pubescent (n = 8, 9)	0	2		

## Statistical analyses

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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 56 weeks of the study regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and death were treatment-emergent AEs (TEAE) that developed/worsened, and death that occurred during TEAE period (the time from the first dose of alirocumab up to the last dose of alirocumab + 70 days [10 weeks]). Analysis was performed on safety population.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Alirocumab 150 mg Q2W
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Reporting group description:

Subjects with BW  $\geq$  50 kg received SC injection of alirocumab 150 mg Q2W for 48 weeks.

Reporting group title	Alirocumab 75 mg Q2W/up to 150 mg Q2W
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Reporting group description:

Subjects with BW < 50 kg received SC injection of alirocumab 75 mg Q2W for 48 weeks. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 in case of increase in BW with BW  $\geq$  50 kg.

Serious adverse events	Alirocumab 150 mg Q2W	Alirocumab 75 mg Q2W/up to 150 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Alirocumab 150 mg Q2W	Alirocumab 75 mg Q2W/up to 150 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	8 / 9 (88.89%)	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Influenza Like Illness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Injection Site Pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Injection Site Reaction			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea Paroxysmal Nocturnal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Thermal Burn subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Congenital, familial and genetic disorders Bicuspid Aortic Valve subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Cardiac disorders Aortic Valve Incompetence subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	2 / 9 (22.22%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	2 / 9 (22.22%) 4	
Blood and lymphatic system disorders Splénomegaly subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1  0 / 9 (0.00%) 0  0 / 9 (0.00%) 0	0 / 9 (0.00%) 0  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1	
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Skin and subcutaneous tissue disorders Dry Skin subjects affected / exposed occurrences (all)  Rash	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Pain In Extremity subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Tendon Pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Tendonitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Influenza subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 9 (22.22%) 2	
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	1 / 9 (11.11%) 1	
Parvovirus B19 Infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Pharyngotonsillitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Metabolism and nutrition disorders			

Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2018	Following amendments were made: Addition of the interactive response technology (IRT) contact performed during Visit 3 (intermediate visit) of the screening period. In addition, several inconsistencies, typographical errors, and other grammatical errors were corrected as well.
11 September 2018	The amendment was done to specify that the optional consent for genotyping was part of the main informed consent form. To address the requests from the Norwegian and Argentinian regulatory agencies for monthly pregnancy tests on all female subjects of childbearing potential throughout the entire study.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported