Clinical trial results:
A Phase 2 Pilot Study with a Randomized Double-Blind Treatment Phase to Evaluate the Pharmacodynamics and Safety of Alirocumab in Patients with Autosomal Dominant Hypercholesterolemia and Gain-of-Function Mutations in 1 or Both Alleles of the PCSK9 Gene or Loss-of-Function Mutations in 1 or More Alleles of the Apolipoprotein B Gene

Summary

EudraCT number	2011-004308-39
Trial protocol	FR
Global end of trial date	28 July 2017

Results information

Result version number	v1
This version publication date	04 August 2019
First version publication date	04 August 2019

Trial information

Trial identification

Sponsor protocol code	R727-CL-1018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01604824
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals
Sponsor organisation address	777 Old Saw Mill, Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, 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	24 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacodynamic effect of alirocumab on serum low-density lipoprotein cholesterol (LDL-C) during 14 weeks of subcutaneous (SC) administered alirocumab in subjects with autosomal dominant hypersholesterolemia (ADH) and gain-of-function mutations (GOFm) in 1 or both alleles of the proprotein convertase subtilisin kexin 9 (PCSK9) gene or with loss-of-function mutations (LOFm) in 1 or more alleles of the apolipoprotein (Apo B) gene.

Protection of trial subjects:

This 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 Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

Stable lipid-lowering therapies (LLT) included, but not limited to statins, ezetimibe, fibrates, niacin, omega-3 fatty acids, and bile acid resins.

Evidence for comparator: -

Actual start date of recruitment	22 February 2012
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	France: 8
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	23
EEA total number of subjects	8

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)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at three sites in France & one in the US. Twenty-eight subjects were screened between Feb 2012 & Apr 2013. A total of 23 subjects were enrolled: 13 in cohort 1 and 10 in cohort 2. Recruitment for cohort 2 occurred after the un-blinding of cohort 1 and analyses of the double-blind study data for cohort 1.

Pre-assignment

Screening details:

Eligible subjects entered a 2-week, single-blind, placebo run-in period (day -14). Cohort 1 (subjects with gain of function mutation [GOFm] in PCSK9 gene) was randomized in a 1:1 ratio (group A or B); cohort 2 (subjects with GOFm in PCSK9 gene or a loss of function mutation [LOFm] in ApoB gene) was also randomized in a 1:1 ratio (group C or D).

Period 1

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

Blinding implementation details:

The double-blind study period includes a double-blind treatment period from visit 3 (day 1) to visit 11 (week 14) and a follow-up period to visit 15 (week 22)

Arms

Are arms mutually exclusive?	Yes
Arm title	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)

Arm description:

Subjects with a gain-of-function mutation (GOFm) in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

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

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

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

Dosage and administration details:

Placebo administered as a SC injection of 1 mL into the abdomen

Arm title	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)

Arm description:

Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

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

Dosage and administration details:

Placebo administered as a SC injection of 1 mL into the abdomen

Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727/SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

Arm title	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)

Arm description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

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

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

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

Dosage and administration details:

Placebo administered as a SC injection of 1 mL into the abdomen

Arm title	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)

Arm description:

Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

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

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

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

Dosage and administration details:

Placebo administered as a SC injection of 1 mL into the abdomen

Number of subjects in period 1	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Started	6	7	5
Completed DB Period (Day 99)	6	7	5
Completed DB Follow-up (Day 155)	6	7	5
Completed	6	7	5

Number of subjects in period 1	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Started	5
Completed DB Period (Day 99)	5
Completed DB Follow-up (Day 155)	5
Completed	5

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PCSK9 GOFm (Cohort 1: Group A and Group B)

Arm description:

Subjects with a GOFm in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC, Q2W for an additional 3 years.

Arm type	Experimental

Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727/SAR236553
Other name	Praluent
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

Arm title	PCSK9 GOFm/ApoB LOFm (Cohort 2: Group C and Group D)

Arm description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects had the possibility to continue in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

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

Dosage and administration details:

Alirocumab 150 mg administered as a SC injection of 1 mL into the abdomen

Number of subjects in period 2	PCSK9 GOFm (Cohort 1: Group A and Group B)	PCSK9 GOFm/ApoB LOFm (Cohort 2: Group C and Group D)
Started	13	10
Started Open-label Extension Period	11	10
Completed Study	10	10
Completed	10	10
Not completed	3	0
Refused to come into office	1	-
Chose not to enter OLE Period	2	-

Baseline characteristics

Reporting groups	
Reporting group title	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)
Reporting group description:	
Subjects with a gain-of-function mutation (GOFm) in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.	
Reporting group title	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)
Reporting group description:	
Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.	
Reporting group title	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Reporting group description:	
Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.	
Reporting group title	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Reporting group description:	
Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.	

Reporting group values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Number of subjects	6	7	5
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)	6	7	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	42.3	46.4	45.6
standard deviation	± 14.72	± 13.24	± 3.21
Gender, Male/Female Units: Subjects			
Male	2	2	1

Female	4	5	4

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	7	5
Race (NIH/OMB) Units: Subjects			
White	5	6	5
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other: Indian Ocean Islander	0	1	0
Other: Mauritius	1	0	0
Measured Low-Density Lipoprotein Cholesterol (LDL-C)			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	108.8	144.3	187.4
standard deviation	± 33.84	± 68.39	± 98.12
Total Cholesterol			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	181.3	216.3	249.8
standard deviation	± 41.89	± 78.61	± 86.68
Non-high-density lipoprotein cholesterol (Non-HDL-C)			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	124.3	165.9	189.4
standard deviation	± 49.00	± 75.59	± 93.43
Apolipoprotein (Apo) B100			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	89.2	101.0	129.4
standard deviation	± 27.29	± 15.77	± 58.27
Apolipoprotein (Apo) A1			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	136.3	131.4	154.0
standard deviation	± 29.75	± 30.02	± 10.98

Reporting group values	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)	Total	
Number of subjects	5	23	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5	23	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42.0		
standard deviation	± 10.84	-	
Gender, Male/Female Units: Subjects			
Male	3	8	
Female	2	15	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	5	23	
Race (NIH/OMB) Units: Subjects			
White	5	21	
Black or African American	0	0	
Asian	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other: Indian Ocean Islander	0	1	
Other: Mauritius	0	1	
Measured Low-Density Lipoprotein Cholesterol (LDL-C)			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	151.0		
standard deviation	± 82.70	-	
Total Cholesterol			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	226.0		
standard deviation	± 77.80	-	
Non-high-density lipoprotein cholesterol (Non-HDL-C)			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	163.4		

standard deviation	± 86.88	-	
Apolipoprotein (Apo) B100			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	103.6		
standard deviation	± 42.83	-	
Apolipoprotein (Apo) A1			
Baseline value is defined as the last available value prior to the first dose of double-blind period (alirocumab or placebo).			
Units: mg/dL			
arithmetic mean	154.8		
standard deviation	± 20.36	-	

End points

End points reporting groups

Reporting group title	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)

Reporting group description:

Subjects with a gain-of-function mutation (GOFm) in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)

Reporting group description:

Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)

Reporting group description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)

Reporting group description:

Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9 GOFm (Cohort 1: Group A and Group B)

Reporting group description:

Subjects with a GOFm in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC, Q2W for an additional 3 years.

Reporting group title	PCSK9 GOFm/ApoB LOFm (Cohort 2: Group C and Group D)

Reporting group description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects had the possibility to continue in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Primary: Percent Change in Measured Serum Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Day 15

End point title	Percent Change in Measured Serum Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Day 15

End point description:

By day 15, subjects in groups A and C had received 1 subcutaneous (SC) dose of 150 mg alirocumab and subjects in group B and D had received 1 SC dose of placebo. [Baseline adjusted least squares (LS) means and standard errors were obtained using analysis of covariance (ANCOVA) model specifying the treatment arm as the fixed effect and the baseline measured LDL-C value as a covariate.]

End point type	Primary

End point timeframe:
Baseline to Day 15

End point values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[1]	7[2]	5[3]	5[4]
Units: percent change				
least squares mean (standard error)	-62.48 (± 8.217)	-8.77 (± 7.575)	-48.21 (± 7.660)	-4.93 (± 7.660)

Notes:
[1] - By day 15, subjects in group A had received 1 SC dose of 150 mg alirocumab
[2] - By day 15, subjects in group B had received 1 SC dose of placebo
[3] - By day 15, subjects in group C had received 1 SC dose of 150 mg alirocumab
[4] - By day 15, subjects in group D had received 1 SC dose of placebo

Statistical analyses

Statistical analysis title	Alirocumab (Group A) vs Placebo (Group B)
Comparison groups	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A) v PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-53.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-79.31
upper limit	-28.12
Variability estimate	Standard error of the mean
Dispersion value	11.486

Notes:
[5] - Threshold for significance ≤ 0.05

Statistical analysis title	Alirocumab (Group C) vs Placebo (Group D)
Comparison groups	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C) v PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-43.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.21
upper limit	17.35
Variability estimate	Standard error of the mean
Dispersion value	10.965

Notes:

[6] - Threshold for significance ≤ 0.05

Secondary: Percent Change in Apolipoprotein (Apo) B100 from Baseline to Day 15

End point title	Percent Change in Apolipoprotein (Apo) B100 from Baseline to Day 15

End point description:

Baseline adjusted LS means and standard errors were obtained using the same ANCOVA model as for pri mary endpoint specifying the treatment arm as the fixed effect and the parameter value as a covariate.

End point type	Secondary

End point timeframe:

Baseline to Day 15

End point values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[7]	7[8]	5[9]	5[10]
Units: percent change				
least squares mean (standard error)				
Apo B100	-53.33 (± 8.678)	-3.78 (± 8.008)	-47.73 (± 7.547)	-3.09 (± 7.547)

Notes:

[7] - By day 15, subjects in group A had received 1 SC dose of 150 mg alirocumab

[8] - By day 15, subjects in group B had received 1 SC dose of placebo

[9] - By day 15, subjects in group C had received 1 SC dose of 150 mg alirocumab

[10] - By day 15, subjects in group D had received 1 SC dose of placebo

Statistical analyses

Statistical analysis title	Alirocumab (Group A) vs Placebo (Group B)

Statistical analysis description:

LS means (SE), mean difference, 95% CI, and p-values were derived from ANCOVA with treatment

group as factor and baseline as covariate.

Comparison groups	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A) v PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-49.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76.39
upper limit	-22.7
Variability estimate	Standard error of the mean
Dispersion value	12.05

Notes:

[11] - Threshold for significance ≤ 0.05

Statistical analysis title	Alirocumab (Group C) vs Placebo (Group D)

Statistical analysis description:

LS means (SE), mean difference, 95% CI, and p-values were derived from ANCOVA with treatment group as factor and baseline as covariate.

Comparison groups	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D) v PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-44.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70.36
upper limit	18.92
Variability estimate	Standard error of the mean
Dispersion value	10.876

Notes:

[12] - Threshold for significance ≤ 0.05

Secondary: Percent Change in Non High-Density Lipoprotein Cholesterol (Non-HDL-C) from Baseline to Day 15

End point title	Percent Change in Non High-Density Lipoprotein Cholesterol (Non-HDL-C) from Baseline to Day 15

End point description:

End point type	Secondary

End point timeframe:
Baseline to Day 15

End point values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[13]	7[14]	5[15]	5[16]
Units: percent change				
least squares mean (standard error)				
Non-HDL-C	-56.87 (± 8.217)	-7.50 (± 7.575)	-44.40 (± 7.357)	-4.04 (± 7.357)

Notes:
[13] - By day 15, subjects in group A had received 1 SC dose of 150 mg alirocumab
[14] - By day 15, subjects in group B had received 1 SC dose of placebo
[15] - By day 15, subjects in group C had received 1 SC dose of 150 mg alirocumab
[16] - By day 15, subjects in group D had received 1 SC dose of placebo

Statistical analyses

Statistical analysis title	Alirocumab (Group A) vs Placebo (Group B)
Comparison groups	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A) v PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-49.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.96
upper limit	-23.77
Variability estimate	Standard error of the mean
Dispersion value	11.487

Notes:
[17] - Threshold for significance ≤ 0.05

Statistical analysis title	Alirocumab (Group C) vs Placebo (Group D)
Comparison groups	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C) v PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063 [18]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-40.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.12
upper limit	15.6
Variability estimate	Standard error of the mean
Dispersion value	10.471

Notes:

[18] - Threshold for significance ≤ 0.05

Secondary: Percent Change in Total Cholesterol (Total-C) from Baseline to Day 15

End point title	Percent Change in Total Cholesterol (Total-C) from Baseline to Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 15

End point values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[19]	7[20]	5[21]	5[22]
Units: percent change				
least squares mean (standard error)				
Total-C	-36.94 (± 5.203)	-6.18 (± 4.802)	-29.40 (± 4.422)	-7.18 (± 4.422)

Notes:

[19] - By day 15, subjects in group A had received 1 SC dose of 150 mg alirocumab

[20] - By day 15, subjects in group B had received 1 SC dose of placebo

[21] - By day 15, subjects in group C had received 1 SC dose of 150 mg alirocumab

[22] - By day 15, subjects in group D had received 1 SC dose of placebo

Statistical analyses

Statistical analysis title	Alirocumab (Group A) vs Placebo (Group B)
Comparison groups	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A) v PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [23]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-30.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.85
upper limit	-14.66
Variability estimate	Standard error of the mean
Dispersion value	7.224

Notes:

[23] - Threshold for significance ≤ 0.05

Statistical analysis title	Alirocumab (Group C) vs Placebo (Group D)
Comparison groups	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C) v PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096 [24]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-22.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.11
upper limit	-7.34
Variability estimate	Standard error of the mean
Dispersion value	6.294

Notes:

[24] - Threshold for significance ≤ 0.05

Secondary: Percent Change in Apolipoprotein (Apo) B100/ ApoA-1 Ratio from Baseline to Day 15

End point title	Percent Change in Apolipoprotein (Apo) B100/ ApoA-1 Ratio from Baseline to Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 15

End point values	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[25]	7[26]	5[27]	5[28]
Units: percent change				
least squares mean (standard error)				
ApoB100/ApoA-1 Ratio	-55.26 (± 7.188)	-5.53 (± 6.647)	-48.34 (± 8.090)	0.99 (± 8.090)

Notes:

[25] - By day 15, subjects in group A had received 1 SC dose of 150 mg alirocumab

[26] - By day 15, subjects in group B had received 1 SC dose placebo

[27] - By day 15, subjects in group C had received 1 SC dose of 150 mg alirocumab

[28] - By day 15, subjects in group D had received 1 SC dose of placebo

Statistical analyses

Statistical analysis title	Alirocumab (Group A) vs Placebo (Group B)
Comparison groups	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A) v PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [29]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-49.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.71
upper limit	-27.74
Variability estimate	Standard error of the mean
Dispersion value	9.867

Notes:

[29] - Threshold for significance ≤ 0.05

Statistical analysis title	Alirocumab (Group C) vs Placebo (Group D)
Comparison groups	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C) v PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2: Group D)
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 [30]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-49.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-76.63
upper limit	-22.03
Variability estimate	Standard error of the mean
Dispersion value	11.545

Notes:

[30] - Threshold for significance ≤ 0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the screening visit after the last alirocumab injection in the open-label period + 70 days through the end of study

Adverse event reporting additional description:

Observation periods for safety analyses: Pretreatment: screening to before 1st injection of alirocumab; Double-blind (DB) treatment-emergent (TE): after 1st through last in DB+70 days; Interim: after last in DB+70 days prior to 1st in open-label (OL). OL TE: after 1st through last in OL+70 days. Post: after last in OL+70 days through end of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)

Reporting group description:

Double-blind Period: Subjects with a GOFm in the PCSK9 gene (Cohort 1: Group A) received 150 mg alirocumab subcutaneously (SC) on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)

Reporting group description:

Subjects with a GOFm in PCSK9 gene (Cohort 1: Group B) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)

Reporting group description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the Apo B gene (Cohort 2: Group C) received 150 mg alirocumab SC on days 1, 15, 29, 43, and 71 and matching placebo SC on days 57, 85, and 99. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2:Group D)

Reporting group description:

Subjects with a GOFm in PCSK9 gene or LOFm in Apo B gene (Cohort 2: Group D) received 150 mg alirocumab SC on days 15, 29, 43, 57, and 85 and matching placebo SC on days 1, 71, and 99 during the double-blind period. Afterwards, subjects continued in an open-label extension period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	OLE Period: PCSK9 GOFm (Cohort 1) Group A & Group B

Reporting group description:

Subjects with a GOFm in PCSK9 gene (Cohort 1): alirocumab 150 mg subcutaneous (SC) injection at Week 0 (Day 1), Week 2 (Day 15), Weeks 4, 6 and 10 (matching placebo at Week 8, 12 and 14) during the double-blind period (Group A) or at Week 2 (Day 15), Weeks 4, 6, 8 and 12 (matching placebo at Week 0 [Day 1], Weeks 10 and 14) during the double-blind period (Group B). Afterwards, subjects continued in an OLE period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Reporting group title	OLE Period: PCSK9 GOFm/ ApoB LOFm (Cohort 2) Group C & Group D

Reporting group description:

Subjects with a GOFm in the PCSK9 gene or a LOFm in the
Apo B gene (Cohort 2): alirocumab 150 mg SC injection at Week 0 (Day 1), Week 2 (Day 15), Weeks 4, 6 and 10 (matching placebo at Weeks 8, 12 and 14) during the double-blind period (Group C) or at Week 2 (Day 15), Weeks 4, 6, 8 and 12 (matching placebo at Week 0 [Day 1], 10 and 14) during the double-blind period (Group D). Afterwards, subjects continued in an OLE period with 150 mg alirocumab SC twice per week (Q2W) for an additional 3 years.

Serious adverse events	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (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
Gastrointestinal disorders			
Salivary gland disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort 2:Group D)	OLE Period: PCSK9 GOFm (Cohort 1) Group A & Group B	OLE Period: PCSK9 GOFm/ ApoB LOFm (Cohort 2) Group C & Group D

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	3 / 11 (27.27%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (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 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (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
Gastrointestinal disorders			
Salivary gland disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (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
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (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	PCSK9 GOFm: Alirocumab from Day 1 (Cohort 1: Group A)	PCSK9 GOFm: Alirocumab from Day 15 (Cohort 1: Group B)	PCSK9 GOFm/ApoB LOFm: Alirocumab from Day1 (Cohort 2: Group C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 7 (85.71%)	5 / 5 (100.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diabetic vascular disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peripheral vascular disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nitrite urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Cardiac procedure complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Angina unstable			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Prinzmetal angina			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Migraine			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Sciatica			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Amnesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diabetic neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nerve compression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyspesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peau d'orange			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	2 / 5 (40.00%)
occurrences (all)	3	1	4
Cystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infectious mononucleosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Kidney infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Otitis externa			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sialoadenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	PCSK9GOFm/ApoB LOFm: Alirocumab from Day 15(Cohort	OLE Period: PCSK9 GOFm (Cohort 1) Group A & Group B	OLE Period: PCSK9 GOFm/ ApoB LOFm (Cohort 2) Group C

	2:Group D)		& Group D
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	10 / 11 (90.91%)	9 / 10 (90.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	10
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diabetic vascular disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Peripheral vascular disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			

subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nitrite urine present			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Cardiac procedure complication			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Joint dislocation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Angina unstable			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Prinzmetal angina			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Migraine			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Amnesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Diabetic neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nerve compression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Ear pruritus			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Dyspesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Functional gastrointestinal disorder			

subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Peau d'orange			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			

Thyroid mass			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Influenza			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	1 / 10 (10.00%)
occurrences (all)	1	4	1
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	4 / 11 (36.36%)	2 / 10 (20.00%)
occurrences (all)	1	6	2
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infectious mononucleosis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Kidney infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Sialoadenitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Vitamin B complex deficiency subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2012	The purpose of this amendment was to: - Update the eligibility criteria to exclude subjects with a known history of active optic nerve disease. - Clarify that subjects who experienced acute injection reactions of clinical concern would be permanently discontinued from study drug.
02 April 2012	The purpose of this amendment was to: - Add a phone call visit (PV5) between visit 5 and visit 6 to ensure the safety of subjects who received their first dose of alirocumab on study day 15 (visit 5). - Remove ribonucleic acid (RNA) sample collection from the study.- Add 2 additional research sample collections to facilitate exploratory research on novel biomarkers. - Remove the pharmacokinetic (PK) sample collection at the screening visit and added an Anti-drug antibody (ADA) sample collection at the screening visit. - Add a request that subjects who were prematurely discontinued from study drug return to the clinic for all remaining study visits'. - Update information about the safety and efficacy for the 3 phase 2 studies in the introduction section. - Update information regarding the requirement that any subject who experienced an acute injection reaction of clinical concern would be permanently discontinued from study drug. - Make clarifications, minor corrections, and administrative changes.
31 October 2012	The purpose of this amendment was to: - Extend the study to include an open-label treatment period for approximately 3 years or until approval of the product. - Add an interim analysis to the study. - Add an independent data monitoring committee (DMC) to the study. - Add an adjudication committee to adjudicate any cardiovascular events that occurred during the study. - Remove "oral" from the body temperature evaluations. - Make clarifications, corrections, and administrative changes.
21 January 2013	The purpose of this amendment was to: - Update information regarding the independent DMC. - Specify that use of red yeast rice was prohibited during the study. - Add additional flow charts to manage AEs and abnormal laboratory values. - Make clarifications, minor corrections, and administrative changes.
23 June 2013	The purpose of this amendment was to: - Include an additional cohort consisting of subjects with Autosomal dominant hypercholesterolemia (ADH) and GOFm in 1 or both alleles of the PCSK9 gene or subjects with LOFm in the Apo B gene (approximately 20 subjects were to be randomized to groups C and D in a 1:1 ratio and subjected to the identical assessments and procedures described for groups A and B in the previous amendment). - Update the document by substituting the non-proprietary name, alirocumab, for REGN727. - Make clarifications, minor corrections, and administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported