



Clinical trial results:

Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial

Summary

EudraCT number	2018-002810-11
Trial protocol	EE BG
Global end of trial date	08 April 2020

Results information

Result version number	v2 (current)
This version publication date	03 July 2021
First version publication date	23 April 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	R727-CL-1609
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03694197
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 8447346643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 8447346643, 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	08 April 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the long term safety of PRALUENT in subjects with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (FH) subjects at high or very high cardiovascular risk who completed the neurocognitive function study R727-CL-1532 (2016-003189-16).

The secondary objectives of the study were:

- To evaluate the effect of PRALUENT on low-density lipoprotein cholesterol (LDL-C)
- To evaluate the effect of PRALUENT on other lipid parameters
- To evaluate the effect of PRALUENT on gonadal steroid hormones

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 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	Bulgaria: 96
Country: Number of subjects enrolled	Estonia: 39
Country: Number of subjects enrolled	Russian Federation: 260
Country: Number of subjects enrolled	South Africa: 304
Country: Number of subjects enrolled	Ukraine: 276
Country: Number of subjects enrolled	United States: 410
Worldwide total number of subjects	1385
EEA total number of subjects	135

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	680
From 65 to 84 years	702
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The 1389 subjects who completed double-blind treatment and the end-of-study (EOS) visit in R727-CL-1532 (2016-003189-16) signed consent and were screened for this open-label study (EOS visit corresponded to day 1/visit 1 of this study).

Pre-assignment

Screening details:

First subcutaneous (SC) injection was administered in the clinic (day 1/visit 1). Four of the 1389 subjects discontinued on day 1 before treatment: 2 discontinued due to failure to meet inclusion/exclusion criteria, 1 withdrew consent, and 1 discontinued due to adverse event (AE). A total of 1385 subjects received any study drug on day 1.

Period 1

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

Arms

Arm title	Alirocumab 75 Q2W/Up150 Q2W
-----------	-----------------------------

Arm description:

All subjects initiated treatment with PRALUENT (alirocumab) at the starting dose of 75 milligrams (mg) once every 2 weeks (Q2W). After week 8, the dose could be adjusted (up to 150 mg Q2W, maintained or from 150 mg Q2W to 75 mg Q2W) if needed based on low-density lipoprotein cholesterol (LDL-C) levels.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SUB74847
Other name	PRALUENT
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

75mg

Number of subjects in period 1	Alirocumab 75 Q2W/Up150 Q2W
Started	1385
Completed	0
Not completed	1385
Physician decision	4
Subject withdrew consent	10
Protocol became inconvenient to participate	1
Related to IMP administration	1
Adverse event, non-fatal	9
Study terminated by sponsor	1350
Subject moved	5

Not disclosed	5
---------------	---

Baseline characteristics

Reporting groups

Reporting group title	Alirocumab 75 Q2W/Up150 Q2W
-----------------------	-----------------------------

Reporting group description:

All subjects initiated treatment with PRALUENT (alirocumab) at the starting dose of 75 milligrams (mg) once every 2 weeks (Q2W). After week 8, the dose could be adjusted (up to 150 mg Q2W, maintained or from 150 mg Q2W to 75 mg Q2W) if needed based on low-density lipoprotein cholesterol (LDL-C) levels.

Reporting group values	Alirocumab 75 Q2W/Up150 Q2W	Total	
Number of subjects	1385	1385	
Age categorical			
Units: Subjects			
Adults (18-64 years)	680	680	
From 65-84 years	702	702	
85 years and over	3	3	
Age Continuous			
Units: Years			
arithmetic mean	64.6		
standard deviation	± 8.63	-	
Sex: Female, Male			
Units: Subjects			
Female	527	527	
Male	858	858	
Race/Ethnicity, Customized			
Race			
Units: Subjects			
White	1178	1178	
Black or African American	81	81	
Asian	7	7	
American Indian or Alaska Native	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Other	118	118	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	10	10	
Not Hispanic or Latino	1372	1372	
Unknown or Not Reported	3	3	

End points

End points reporting groups

Reporting group title	Alirocumab 75 Q2W/Up150 Q2W
Reporting group description:	
All subjects initiated treatment with PRALUENT (alirocumab) at the starting dose of 75 milligrams (mg) once every 2 weeks (Q2W). After week 8, the dose could be adjusted (up to 150 mg Q2W, maintained or from 150 mg Q2W to 75 mg Q2W) if needed based on low-density lipoprotein cholesterol (LDL-C) levels.	

Primary: Number of subjects with adverse events (AE) after first administration of study drug through the last dose of study drug plus 2 weeks

End point title	Number of subjects with adverse events (AE) after first administration of study drug through the last dose of study drug plus 2 weeks ^[1]
-----------------	--

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. AEs include serious adverse events (SAEs), AEs leading to treatment discontinuation, and adverse events of special interest (AESI). AESI include local injection site reactions, general allergic events, elevated alanine aminotransferase (ALT) levels greater than or equal to (\geq) 3 upper limit normal (ULN) (if baseline is less than ($<$) ULN)/ALT $\geq 2 \times$ ULN (if baseline \geq ULN), neurologic events, neurocognitive events (according to Customized Medical Dictionary for Regulatory Activities [MedDRA] Query [CMQ] by Sponsor grouping and CMQ by FDA grouping), cataract, new onset diabetes (NOD), hepatic disorders, and diabetes mellitus (DM)/diabetic complications.

End point type	Primary
----------------	---------

End point timeframe:

After first administration of study drug through the last dose of study drug plus 2 weeks, up to 80 weeks; Safety analysis set (SAF): All subjects who received any study drug

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: No formal inferential testing was performed.

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Subjects				
Any treatment emergent AE (TEAE)	568			
Any treatment emergent serious AE (SAE)	89			
Any TEAE leading to death	5			
Any TEAE leading to perm. treatment discount.	9			
Any neurocognitive disorders TEAE (by Sponsor CMQ)	4			
Any neurocognitive disorders TEAE (by FDA CMQ)	0			
Any NOD; n=687 (w/out diabetes at baseline)	15			
Any hepatic disorders TEAE	14			
Any neurological TEAE	15			
Any general allergic TEAE	25			

At least one TE injection site reaction	22			
Any cataract TEAE	5			
Any elevated ALT ≥ 3 ULN	1			
Any DM/DC TEAE; n=698 (with diabetes at baseline)	41			
Any DM/DC TEAE; n=687 (w/out diabetes at baseline)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated low-density lipoprotein cholesterol (LDL-C) values from baseline over time

End point title	Calculated low-density lipoprotein cholesterol (LDL-C) values from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); Safety analysis set (SAF): All subjects who received any study drug; Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Milligrams per decilitre (mg/dL)				
arithmetic mean (standard deviation)				
Baseline (n = 1367)	117.8 (\pm 40.67)			
Week 8 (n = 1345)	58.9 (\pm 37.31)			
Week 12 (n = 356)	63.6 (\pm 40.79)			
Week 24 (n = 769)	56.2 (\pm 36.59)			
Week 48 (n = 311)	56.8 (\pm 36.13)			
Week 72 (n = 54)	52.2 (\pm 38.80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in LDL-C from baseline over time

End point title	Percent change in LDL-C from baseline over time
-----------------	---

End point description:

SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 1328)	-48.74 (± 31.121)			
Week 12 (n = 353)	-44.64 (± 35.338)			
Week 24 (n = 754)	-50.75 (± 30.249)			
Week 48 (n = 301)	-52.35 (± 27.929)			
Week 72 (n = 54)	-51.21 (± 32.742)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total cholesterol (Total-C) values from baseline over time

End point title	Total cholesterol (Total-C) values from baseline over time
-----------------	--

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				

Baseline (n = 1385)	199.5 (± 48.88)			
Week 8 (n = 1346)	139.5 (± 44.76)			
Week 12 (n = 356)	145.0 (± 48.68)			
Week 24 (n = 769)	137.3 (± 44.18)			
Week 48 (n = 311)	139.5 (± 44.53)			
Week 72 (n = 54)	131.7 (± 43.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Total-C over time

End point title	Percent change from baseline in Total-C over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 1346)	-28.68 (± 20.158)			
Week 12 (n = 356)	-25.99 (± 23.058)			
Week 24 (n = 769)	-29.98 (± 20.930)			
Week 48 (n = 311)	-30.89 (± 21.004)			
Week 72 (n = 54)	-31.55 (± 22.238)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lipoprotein-a (Lp(a)) values from baseline over time

End point title	Lipoprotein-a (Lp(a)) values from baseline over time
-----------------	--

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	39.7 (± 47.86)			
Week 8 (n = 190)	35.0 (± 41.99)			
Week 12 (n = 353)	32.7 (± 39.42)			
Week 24 (n = 419)	33.9 (± 42.54)			
Week 48 (n = 311)	38.6 (± 50.66)			
Week 72 (n = 54)	40.4 (± 56.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Lp(a) over time

End point title	Percent change from baseline in Lp(a) over time
-----------------	---

End point description:

SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				

Week 8 (n = 190)	-12.69 (± 35.452)			
Week 12 (n = 353)	10.63 (± 228.659)			
Week 24 (n = 419)	-6.80 (± 110.827)			
Week 48 (n = 311)	-7.89 (± 116.831)			
Week 72 (n = 54)	-22.23 (± 28.233)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-high-density lipoprotein cholesterol (non-HDL-C) values from baseline over time

End point title	Non-high-density lipoprotein cholesterol (non-HDL-C) values from baseline over time
-----------------	---

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	152.4 (± 48.81)			
Week 8 (n = 1346)	88.5 (± 43.54)			
Week 12 (n = 356)	94.3 (± 48.77)			
Week 24 (n = 769)	87.3 (± 43.56)			
Week 48 (n = 311)	88.9 (± 44.25)			
Week 72 (n = 54)	80.9 (± 42.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in non-HDL-C over time

End point title	Percent change from baseline in non-HDL-C over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 1346)	-40.35 (± 27.470)			
Week 12 (n = 356)	-36.89 (± 29.567)			
Week 24 (n = 769)	-41.47 (± 26.763)			
Week 48 (n = 311)	-42.33 (± 28.728)			
Week 72 (n = 54)	-43.28 (± 29.534)			

Statistical analyses

No statistical analyses for this end point

Secondary: High-density lipoprotein cholesterol (HDL-C) values from baseline over time

End point title	High-density lipoprotein cholesterol (HDL-C) values from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	47.1 (± 13.92)			
Week 8 (n = 1346)	51.0 (± 14.82)			
Week 12 (n = 356)	50.6 (± 13.95)			
Week 24 (n = 769)	49.9 (± 14.80)			
Week 48 (n = 311)	50.5 (± 14.66)			
Week 72 (n = 54)	50.8 (± 14.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in HDL-C over time

End point title	Percent change from baseline in HDL-C over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 1346)	10.54 (± 22.735)			
Week 12 (n = 356)	10.33 (± 21.933)			
Week 24 (n = 769)	8.53 (± 21.824)			
Week 48 (n = 311)	9.81 (± 23.690)			
Week 72 (n = 54)	9.24 (± 21.505)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting triglycerides (TGs) values from baseline over time

End point title	Fasting triglycerides (TGs) values from baseline over time
-----------------	--

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	179.2 (± 146.51)			
Week 8 (n = 1346)	154.8 (± 113.05)			
Week 12 (n = 356)	162.2 (± 182.00)			
Week 24 (n = 769)	169.3 (± 161.45)			
Week 48 (n = 311)	171.1 (± 131.35)			
Week 72 (n = 54)	156.9 (± 65.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in fasting TGs over time

End point title	Percent change from baseline in fasting TGs over time
-----------------	---

End point description:

SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 1346)	-4.68 (± 49.230)			
Week 12 (n = 356)	-4.29 (± 40.748)			
Week 24 (n = 769)	0.42 (± 54.118)			
Week 48 (n = 311)	1.54 (± 69.156)			
Week 72 (n = 54)	-5.97 (± 41.440)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apolipoprotein B (Apo B) values from baseline over time

End point title	Apolipoprotein B (Apo B) values from baseline over time
End point description:	
The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16). SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	103.8 (± 27.25)			
Week 8 (n = 190)	62.5 (± 27.63)			
Week 12 (n = 353)	68.0 (± 31.32)			
Week 24 (n = 420)	61.5 (± 26.20)			
Week 48 (n = 311)	63.7 (± 26.40)			
Week 72 (n = 54)	58.5 (± 25.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Apo B over time

End point title	Percent change from baseline in Apo B over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 190)	-36.51 (± 34.460)			
Week 12 (n = 353)	-34.48 (± 27.905)			
Week 24 (n = 420)	-38.16 (± 24.867)			
Week 48 (n = 311)	-37.93 (± 23.767)			
Week 72 (n = 54)	-39.04 (± 26.383)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apolipoprotein-A1 (Apo A1) values from baseline over time

End point title	Apolipoprotein-A1 (Apo A1) values from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16). SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	145.3 (± 24.95)			
Week 8 (n = 190)	148.5 (± 24.73)			
Week 12 (n = 353)	149.4 (± 25.38)			
Week 24 (n = 420)	150.7 (± 26.36)			
Week 48 (n = 311)	152.6 (± 25.96)			
Week 72 (n = 54)	151.4 (± 26.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Apo A1 over time

End point title	Percent change from baseline in Apo A1 over time
End point description:	
SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 8 (n = 190)	5.07 (± 13.385)			
Week 12 (n = 353)	2.99 (± 13.638)			
Week 24 (n = 420)	5.35 (± 14.108)			
Week 48 (n = 311)	4.77 (± 13.836)			
Week 72 (n = 54)	1.21 (± 13.170)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gonadal hormone (follicle stimulating hormone [FSH] and luteinizing hormone [LH]) values for female subjects from baseline over time

End point title	Gonadal hormone (follicle stimulating hormone [FSH] and luteinizing hormone [LH]) values for female subjects from baseline over time
End point description:	The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (Female subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint
End point type	Secondary
End point timeframe:	Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	527			
Units: International units per litre (IU/L)				
arithmetic mean (standard deviation)				
FSH Baseline (n = 527)	57.948 (± 26.7383)			
FSH Week 8 (n = 84)	59.264 (± 24.7912)			
FSH Week 12 (n = 135)	54.279 (± 23.9923)			
FSH Week 24 (n = 280)	57.664 (± 25.9830)			
FSH Week 48 (n = 106)	56.529 (± 25.1408)			
FSH Week 72 (n = 23)	58.600 (± 24.5205)			
LH Baseline (n = 527)	30.155 (± 13.1090)			
LH Week 8 (n = 84)	33.794 (± 14.4459)			
LH Week 12 (n = 135)	30.779 (± 13.0946)			
LH Week 24 (n = 280)	31.260 (± 13.7344)			
LH Week 48 (n = 106)	29.585 (± 13.9792)			
LH Week 72 (n = 23)	29.248 (± 11.0829)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in gonadal hormones (FSH and LH) for female subjects over time

End point title	Change from baseline in gonadal hormones (FSH and LH) for female subjects over time
-----------------	---

End point description:

SAF (Female subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	527			
Units: IU/L				
arithmetic mean (standard deviation)				
FSH Week 8 (n = 84)	-0.765 (± 12.0083)			
FSH Week 12 (n = 135)	-0.984 (± 12.1584)			
FSH Week 24 (n = 280)	-0.575 (± 8.7780)			
FSH Week 48 (n = 106)	-0.877 (± 15.9972)			
FSH Week 72 (n = 23)	-1.861 (± 8.6119)			
LH Week 8 (n = 84)	2.730 (± 8.2258)			
LH Week 12 (n = 135)	1.882 (± 8.2884)			
LH Week 24 (n = 280)	0.939 (± 6.3694)			
LH Week 48 (n = 106)	0.367 (± 8.5631)			
LH Week 72 (n = 23)	0.222 (± 6.8910)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gonadal (FSH and LH) hormone values for male subjects from baseline over time

End point title	Gonadal (FSH and LH) hormone values for male subjects from baseline over time
-----------------	---

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (Male subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	858			
Units: International units per litre (IU/L)				
arithmetic mean (standard deviation)				
FSH Baseline (n = 858)	8.006 (± 7.4451)			
FSH Week 8 (n = 117)	7.959 (± 7.5500)			
FSH Week 12 (n = 215)	7.766 (± 6.8204)			
FSH Week 24 (n = 489)	8.268 (± 8.1355)			
FSH Week 48 (n = 203)	9.597 (± 11.2138)			
FSH Week 72 (n = 32)	10.005 (± 13.2973)			
LH Baseline (n = 858)	6.500 (± 4.2832)			
LH Week 8 (n = 117)	7.094 (± 4.7226)			
LH Week 12 (n = 215)	6.688 (± 4.4079)			
LH Week 24 (n = 489)	6.931 (± 4.8597)			
LH Week 48 (n = 203)	7.677 (± 6.5478)			
LH Week 72 (n = 32)	8.173 (± 8.9083)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in gonadal hormones (FSH and LH) for male subjects over time

End point title	Change from baseline in gonadal hormones (FSH and LH) for male subjects over time
End point description: SAF (Male subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	858			
Units: IU/L				
arithmetic mean (standard deviation)				
FSH Week 8 (n = 117)	0.285 (± 3.7264)			
FSH Week 12 (n = 215)	-0.598 (± 4.1076)			
FSH Week 24 (n = 489)	0.331 (± 6.0522)			
FSH Week 48 (n = 203)	0.960 (± 10.3803)			
FSH Week 72 (n = 32)	2.458 (± 13.4730)			
LH Week 8 (n = 117)	0.535 (± 2.4847)			
LH Week 12 (n = 215)	-0.136 (± 3.2638)			
LH Week 24 (n = 489)	0.582 (± 4.4964)			
LH Week 48 (n = 203)	1.015 (± 6.6344)			
LH Week 72 (n = 32)	1.964 (± 9.3028)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gonadotropin (estradiol) values for female subjects from baseline over time

End point title	Gonadotropin (estradiol) values for female subjects from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (Female subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	527			
Units: picomoles per litre (pmol/L)				
arithmetic mean (standard deviation)				
Baseline (n = 527)	55.589 (\pm 80.8238)			
Week 8 (n = 84)	58.676 (\pm 69.0119)			
Week 12 (n = 135)	59.673 (\pm 74.7587)			
Week 24 (n = 280)	64.304 (\pm 103.8955)			
Week 48 (n = 106)	64.503 (\pm 102.1595)			
Week 72 (n = 23)	57.926 (\pm 67.1795)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in gonadotropins (estradiol) for female subjects over time

End point title	Change from baseline in gonadotropins (estradiol) for female subjects over time
End point description: SAF (Female subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	527			
Units: pmol/L				
arithmetic mean (standard deviation)				
Week 8 (n = 84)	4.272 (\pm 77.1561)			
Week 12 (n = 135)	9.262 (\pm 73.1050)			

Week 24 (n = 280)	7.869 (± 78.4151)			
Week 48 (n = 106)	11.763 (± 97.5350)			
Week 72 (n = 23)	9.569 (± 38.0952)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gonadotropin (testosterone) values for male subjects from baseline over time

End point title	Gonadotropin (testosterone) values for male subjects from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (Male subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	858			
Units: nanomoles per litre (nmol/L)				
arithmetic mean (standard deviation)				
Baseline (n = 858)	13.4370 (± 6.36321)			
Week 8 (n = 117)	14.5802 (± 5.99821)			
Week 12 (n = 215)	14.2443 (± 6.77070)			
Week 24 (n = 489)	13.5818 (± 6.11269)			
Week 48 (n = 203)	13.4798 (± 7.04977)			
Week 72 (n = 32)	12.7538 (± 6.37408)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in gonadotropins (testosterone) for male subjects over time

End point title	Change from baseline in gonadotropins (testosterone) for male subjects over time
End point description: SAF (Male subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	858			
Units: nmol/L				
arithmetic mean (standard deviation)				
Week 8 (n = 117)	0.6030 (\pm 4.46401)			
Week 12 (n = 215)	0.7965 (\pm 4.74765)			
Week 24 (n = 489)	0.1946 (\pm 5.89220)			
Week 48 (n = 203)	0.0498 (\pm 6.34201)			
Week 72 (n = 32)	1.2569 (\pm 5.29335)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine aminotransferase values from baseline over time

End point title	Alanine aminotransferase values from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: Units per Liter (U/L)				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	0.516 (± 0.3218)			
Week 8 (n = 201)	0.468 (± 0.2745)			
Week 12 (n = 350)	0.505 (± 0.4940)			
Week 24 (n = 769)	0.493 (± 0.2851)			
Week 48 (n = 310)	0.533 (± 0.3267)			
Week 72 (n = 54)	0.468 (± 0.2340)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in alanine aminotransferase over time

End point title	Change from baseline in alanine aminotransferase over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: U/L				
arithmetic mean (standard deviation)				
Week 8 (n = 201)	-0.025 (± 0.3006)			
Week 12 (n = 350)	0.009 (± 0.5189)			
Week 24 (n = 769)	-0.036 (± 0.3294)			
Week 48 (n = 310)	-0.027 (± 0.3052)			
Week 72 (n = 54)	-0.062 (± 0.1872)			

Statistical analyses

No statistical analyses for this end point

Secondary: Aspartate aminotransferase values from baseline over time

End point title	Aspartate aminotransferase values from baseline over time
-----------------	---

End point description:

The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 72

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	0.553 (± 0.2516)			
Week 8 (n = 201)	0.520 (± 0.2536)			
Week 12 (n = 350)	0.527 (± 0.2698)			
Week 24 (n = 769)	0.544 (± 0.3071)			
Week 48 (n = 310)	0.565 (± 0.2773)			
Week 72 (n = 54)	0.556 (± 0.2256)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in aspartate aminotransferase over time

End point title	Change from baseline in aspartate aminotransferase over time
-----------------	--

End point description:

SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: U/L				
arithmetic mean (standard deviation)				
Week 8 (n = 201)	-0.022 (± 0.2856)			
Week 12 (n = 350)	-0.017 (± 0.3004)			
Week 24 (n = 769)	-0.013 (± 0.2901)			
Week 48 (n = 310)	-0.019 (± 0.2390)			
Week 72 (n = 54)	-0.037 (± 0.1730)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alkaline phosphatase values from baseline over time

End point title	Alkaline phosphatase values from baseline over time
End point description:	
The baseline value was defined as the last available value before the first dose of double-blind study treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	0.601 (± 0.1865)			
Week 8 (n = 201)	0.635 (± 0.2151)			

Week 12 (n = 350)	0.605 (± 0.1865)			
Week 24 (n = 769)	0.602 (± 0.2012)			
Week 48 (n = 310)	0.602 (± 0.2657)			
Week 72 (n = 54)	0.553 (± 0.1678)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in alkaline phosphatase over time

End point title	Change from baseline in alkaline phosphatase over time
End point description: SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe: Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: U/L				
arithmetic mean (standard deviation)				
Week 8 (n = 201)	0.009 (± 0.1371)			
Week 12 (n = 350)	0.013 (± 0.1203)			
Week 24 (n = 769)	0.006 (± 0.1152)			
Week 48 (n = 310)	0.024 (± 0.2333)			
Week 72 (n = 54)	-0.011 (± 0.1029)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total bilirubin values from baseline over time

End point title	Total bilirubin values from baseline over time
End point description: The baseline value was defined as the last available value before the first dose of double-blind study	

treatment in study R727-CL-1532 (2016-003189-16); SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint

End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: micromoles per litre (umol/L)				
arithmetic mean (standard deviation)				
Baseline (n = 1385)	10.76 (± 4.736)			
Week 8 (n = 201)	10.01 (± 4.123)			
Week 12 (n = 350)	10.26 (± 4.758)			
Week 24 (n = 769)	10.41 (± 4.922)			
Week 48 (n = 310)	10.06 (± 4.503)			
Week 72 (n = 54)	8.82 (± 3.770)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total bilirubin over time

End point title	Change from baseline in total bilirubin over time
End point description:	
SAF (All subjects who received any study drug); Here, "n" = number of subjects evaluable at that timepoint	
End point type	Secondary
End point timeframe:	
Up to week 72	

End point values	Alirocumab 75 Q2W/Up150 Q2W			
Subject group type	Reporting group			
Number of subjects analysed	1385			
Units: umol/L				
arithmetic mean (standard deviation)				
Week 8 (n = 201)	-0.37 (± 3.120)			

Week 12 (n = 350)	-0.44 (± 3.854)			
Week 24 (n = 769)	-0.48 (± 3.962)			
Week 48 (n = 310)	-0.05 (± 3.991)			
Week 72 (n = 54)	0.71 (± 2.152)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time of signed informed consent until the end of study, up to 80 weeks.

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are reported. TEAEs are AEs that developed or worsened or became serious during the TEAE period (time from first dose of study drug to the last study visit).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.0
--------------------	------

Reporting groups

Reporting group title	Alirocumab 75 Q2W/Up150 Q2W
-----------------------	-----------------------------

Reporting group description:

All subjects initiated treatment with PRALUENT (alirocumab) at the starting dose of 75 milligrams (mg) once every 2 weeks (Q2W). After week 8, the dose could be adjusted (up to 150 mg Q2W, maintained or from 150 mg Q2W to 75 mg Q2W) if needed based on low-density lipoprotein cholesterol (LDL-C) levels.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No occurrence of non-serious adverse events met the 5% threshold for reporting.

Serious adverse events	Alirocumab 75 Q2W/Up150 Q2W		
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 1385 (6.43%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Synovial sarcoma			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive urgency			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery occlusion			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 1385 (0.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Non-cardiac chest pain			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis chronic			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paranasal cyst			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar disorder			

subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cartilage injury			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electric shock			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haemorrhage			

subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	10 / 1385 (0.72%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	8 / 1385 (0.58%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	6 / 1385 (0.43%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	5 / 1385 (0.36%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Acute left ventricular failure			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			

subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure chronic			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Carotid artery disease			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery occlusion			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis chronic			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 1385 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscle spasms			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 1385 (0.29%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendiceal abscess			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cholecystitis infective			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia staphylococcal			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 1385 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Alirocumab 75 Q2W/Up150 Q2W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1385 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2018	The protocol was amended to align with feedback received from the European Medicines Agency (EMA), and updated for clarity and consistency with R727-CL-1532 (2016-003189-16) neurocognitive function protocol Amendment 5.
17 September 2018	The protocol was amended to add back text that was inadvertently removed in protocol amendment 1, and to clarify language for blinding, study discontinuation, treatment compliance, adverse event (AE) reporting period, and procedures for reporting serious adverse events (SAEs).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported