Clinical trial results:
A Multi-Country, Multicenter, Single-Arm, Open-Label Study to Document the Safety, Tolerability and Effect of Alirocumab on Atherogenic Lipoproteins in High Cardio-Vascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies

Summary

EudraCT number	2015-000620-28
Trial protocol	DK CZ SK BE IT HU AT DE FR SE ES FI PL GR SI
Global end of trial date	12 April 2019

Results information

Result version number	v1 (current)
This version publication date	25 April 2020
First version publication date	25 April 2020

Trial information

Trial identification

Sponsor protocol code	LPS14245

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02476006
WHO universal trial number (UTN)	U1111-1163-0984
Other trial identifiers	Study Name: ODYSSEY APPRISE

Notes:

Sponsors

Sponsor organisation name	Sanofi-Aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	28 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide access to alirocumab ahead of commercial availability and to document the overall safety and tolerability of alirocumab in subjects with severe hypercholesterolemia at risk for subsequent cardiovascular (CV) events and not adequately controlled with currently available lipid-modifying therapy (LMT).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 131
Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Spain: 92
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Belgium: 68
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 215
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 10

Country: Number of subjects enrolled	Italy: 255
Worldwide total number of subjects	994
EEA total number of subjects	833

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)	722
From 65 to 84 years	269
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 156 sites in 17 countries. A total of 1305 subjects were screened between 23-June-2015 to 27-December 2016, of whom 307 were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

A total of 998 subjects were enrolled in the study. Out of which, 994 subjects were treated.

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

Arm description:

Subjects received Alirocumab 150 milligram (mg) subcutaneously (SC) once every two weeks (Q2W) or 75 mg SC Q2W added to stable LMT up to a maximum of 120 weeks. Alirocumab dose was either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W, based on Investigator judgment and treatment response.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	Praluent®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received Alirocumab 150 mg or 75 mg SC Q2W as per Investigator judgement in the abdomen, thigh, or outer area of upper arm.

Number of subjects in period 1	Alirocumab
Started	994
Treated	994
Completed	878
Not completed	116
Adverse Event	41
Physician Decision	5
Poor compliance to study protocol	3
Sponsor decision	6
Excluded from study	1
Switched to commercial drug	4
Study ended treatment not available	4

Death	4
Lost to Follow-up	5
Pregnancy	1
Subject did not wish to continue	39
Protocol Violation	1
Lack of treatment efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Alirocumab
Reporting group description:	
Subjects received Alirocumab 150 milligram (mg) subcutaneously (SC) once every two weeks (Q2W) or 75 mg SC Q2W added to stable LMT up to a maximum of 120 weeks. Alirocumab dose was either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W, based on Investigator judgment and treatment response.	

Reporting group values	Alirocumab	Total	
Number of subjects	994	994	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 56.6 ± 11.7	 -	
Gender categorical Units: Subjects			
Female	369	369	
Male	625	625	
Race Units: Subjects			
White/Caucasian	969	969	
Black	10	10	
Asian/Oriental	6	6	
Multiracial	1	1	
Other	8	8	

End points

End points reporting groups

Reporting group title	Alirocumab

Reporting group description:

Subjects received Alirocumab 150 milligram (mg) subcutaneously (SC) once every two weeks (Q2W) or 75 mg SC Q2W added to stable LMT up to a maximum of 120 weeks. Alirocumab dose was either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W, based on Investigator judgment and treatment response.

Primary: Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

Adverse Event (AE) was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. TEAEs were defined as AEs that that developed or worsened or became serious during the TEAE period (time from the first injection of study drug up to the day of the last injection of study drug + 14 days). A Serious Adverse Event (SAE) was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Analysis was performed on safety population that included all subjects who had signed the informed consent form and who had received at least one dose or partial dose of alirocumab.

End point type	Primary

End point timeframe:

From first injection of investigational medicinal product (IMP) up to 2 weeks after last dose of study drug (Week 120)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	994			
Units: percentage of subjects				
number (not applicable)				
Any TEAE	71.6			
Any treatment emergent SAE	16.2			
Any TEAE leading to death	0.2			
Any TEAE leading to treatment discontinuation	4.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Calculated Low Density Lipoprotein Cholesterol (LDL-C) at Week 12

End point title	Percent Change From Baseline in Calculated Low Density Lipoprotein Cholesterol (LDL-C) at Week 12

End point description:

Calculated LDL-C values were obtained using the Friedewald formula. Calculated LDL-C in mg/dL from Friedewald formula (LDL cholesterol = Total cholesterol - HDL cholesterol - [Triglyceride/5]). Baseline value was defined as the last observation before the first dose of the treatment. Analysis was performed on modified intent-to-treat population (mITT): all enrolled subjects who received at least one dose or part of a dose of alirocumab and had an evaluable efficacy endpoint during the efficacy treatment period (defined as time period from the first injection of alirocumab up to the day of last injection +21 days).

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percent change				
arithmetic mean (standard deviation)	-54.84 (± 20.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12

End point title	Percentage of Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12

End point description:

LDL-Cholesterol was calculated using the Friedewald formula. Percentage of subjects who reached calculated LDL-C <100 mg/dL (2.59 millimoles per litre [mmol/L]) at week 12 were reported. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percentage of subjects				
number (confidence interval 95%)	74.6 (71.7 to 77.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12

End point title	Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12

End point description:

LDL-Cholesterol was calculated using the Friedewald formula. Percentage of subjects who reached calculated LDL-C <70 mg/dL (1.81 mmol/L) at week 12 were reported. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percentage of subjects				
number (confidence interval 95%)	50.2 (46.9 to 53.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or >=50% Reduction From Baseline in LDL-C at Week 12

End point title	Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or >=50% Reduction From Baseline in LDL-C at Week 12

End point description:

LDL-Cholesterol was calculated using the Friedewald formula. Percentage of subjects who reached LDL-C <70 mg/dL at Week 12 and/or >=50% reduction from baseline in LDL-C at Week 12 are reported. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percentage of subjects				
number (confidence interval 95%)	69.1 (66.0 to 72.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 12

End point title	Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 12

End point description:

Baseline value was defined as the last observation before the first dose of the treatment. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percent change				
arithmetic mean (standard deviation)	-45.89 (± 35.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Cholesterol (Total-C) at Week 12

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Week 12

End point description:

Baseline value was defined as the last observation before the first dose of the treatment. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percent change				
arithmetic mean (standard deviation)	-38.28 (± 15.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in High Density Lipoprotein Cholesterol at Week 12

End point title	Percent Change From Baseline in High Density Lipoprotein Cholesterol at Week 12

End point description:

Baseline value was defined as the last observation before the first dose of the treatment. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percent change				
arithmetic mean (standard deviation)	4.37 (± 17.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Triglycerides at Week 12

End point title	Percent Change From Baseline in Triglycerides at Week 12

End point description:

Baseline value was defined as the last observation before the first dose of the treatment. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	921			
Units: percent change				
arithmetic mean (standard deviation)	-8.28 (± 33.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Subject's Acceptability of Self-Injection Using Self Injection Assessment Questionnaire (SIAQ): Feeling About Injections, Self Confidence, Satisfaction With Self-Injections

End point title	Assessment of Subject's Acceptability of Self-Injection Using Self Injection Assessment Questionnaire (SIAQ): Feeling About Injections, Self Confidence, Satisfaction With Self-Injections

End point description:

Pre-SIAQ: consisted of 7 items grouped into 3 domains: feelings about injections, self-confidence & satisfaction with self-injection. Post-SIAQ: 21 items grouped into 6 domains: feelings about injections, self-image, self-confidence, injection-site reactions, ease of use & satisfaction with self-injection. Subjects rated each item on 5-point (or 6-point) semantic Likert-type scale, where lower numbers=worse experience. Item scores were transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience). Transformed scores for items contributing to a domain were then averaged into a domain score. Each domain score ranges from 0 (worst experience) to 10 (best experience). Pre & Post-SIAQ population: subjects from the safety population who self-injected the training injection & completed a Pre-SIAQ before first self-injection, who self-injected IMP at least once during the study and completed a Post-SIAQ. Here,"n"=subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline (Pre-SIAQ), Week 4, Week 8, Week 12, Week 24, Week 48, Week 72, Week 96

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	952			
Units: units on a scale				
arithmetic mean (standard deviation)				
Feelings about injections: Baseline (n=952)	8.6 (± 1.8)			
Feelings about injections: Week 4 (n=909)	9.1 (± 1.4)			
Feelings about injections: Week 8 (n=894)	9.1 (± 1.4)			
Feelings about injections: Week 12 (n=847)	9.2 (± 1.4)			

Feelings about injections: Week 24 (n=668)	9.2 (± 1.4)			
Feelings about injections: Week 48 (n=547)	9.2 (± 1.4)			
Feelings about injections: Week 72 (n=423)	9.2 (± 1.4)			
Feelings about injections: Week 96 (n=343)	9.3 (± 1.3)			
Self confidence: Baseline (n=943)	6.9 (± 2.4)			
Self confidence: Week 4 (n=905)	8.0 (± 2.1)			
Self confidence: Week 8 (n=889)	8.1 (± 2.0)			
Self confidence: Week 12 (n=844)	8.1 (± 1.9)			
Self confidence: Week 24 (n=666)	8.0 (± 2.1)			
Self confidence: Week 48 (n=548)	8.1 (± 2.1)			
Self confidence: Week 72 (n=420)	8.3 (± 2.0)			
Self confidence: Week 96 (n=340)	8.4 (± 2.0)			
Satisfaction with self injection: Baseline (n=918)	7.2 (± 2.5)			
Satisfaction with self-injections: Week 4 (n=906)	8.5 (± 1.6)			
Satisfaction with self-injections: Week 8 (n=889)	8.7 (± 1.6)			
Satisfaction with self-injections: Week 12 (n=842)	8.7 (± 1.6)			
Satisfaction with self-injections: Week 24 (n=667)	8.6 (± 1.8)			
Satisfaction with self-injections: Week 48 (n=542)	8.7 (± 1.5)			
Satisfaction with self-injections: Week 72 (n=418)	8.8 (± 1.7)			
Satisfaction with self-injections: Week 96 (n=338)	8.8 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Subject's Acceptability of Self-Injection Using Self Injection Assessment Questionnaire (SIAQ): Self Image, Injection-Site Reactions, Ease of Use

End point title	Assessment of Subject's Acceptability of Self-Injection Using Self Injection Assessment Questionnaire (SIAQ): Self Image, Injection-Site Reactions, Ease of Use

End point description:

Post-SIAQ: self-completed after self-injection, consisted of 21 items grouped into 6 domains: feelings about injections, self-image, self-confidence, injection-site reactions, ease of use & satisfaction with self-injection. Subjects rated each item on 5-point (or 6-point) semantic Likert-type scale, where lower numbers=worse experience. Item scores were transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item. Transformed scores for items contributing to a domain were then averaged into a domain score. Each domain score ranges from 0 (worst experience) to 10 (best experience). Domain scores which are not in common with Pre-SIAQ were analyzed on the Post-SIAQ population and are reported here. POST-SIAQ population: subjects from safety population who self-injected at least once during the study and completed a POST-SIAQ regardless of completion of PRE-SIAQ. Here, 'n'= subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Week 4, Week 8, Week 12, Week 24, Week 48, Week 72, Week 96

End point values	Alirocumab			
Subject group type	Reporting group			
Number of subjects analysed	979			
Units: units on a scale				
arithmetic mean (standard deviation)				
Self Image: Week 4 (n=929)	9.4 (± 1.4)			
Self Image: Week 8 (n=915)	9.4 (± 1.4)			
Self Image: Week 12 (n=866)	9.4 (± 1.4)			
Self Image: Week 24 (n=682)	9.3 (± 1.5)			
Self Image: Week 48 (n=560)	9.4 (± 1.4)			
Self Image: Week 72 (n=433)	9.3 (± 1.5)			
Self Image: Week 96 (n=349)	9.4 (± 1.4)			
Injection-site reactions: Week 4 (n=925)	9.6 (± 0.7)			
Injection-site reactions: Week 8 (n=907)	9.6 (± 0.8)			
Injection-site reactions: Week 12 (n=862)	9.6 (± 0.7)			
Injection-site reactions: Week 24 (n=679)	9.5 (± 0.9)			
Injection-site reactions: Week 48 (n=549)	9.5 (± 0.8)			
Injection-site reactions: Week 72 (n=431)	9.5 (± 0.8)			
Injection-site reactions: Week 96 (n=353)	9.5 (± 0.8)			
Ease of use: Week 4 (n=927)	8.7 (± 1.5)			
Ease of use: Week 8 (n=914)	8.7 (± 1.6)			
Ease of use: Week 12 (n=866)	8.8 (± 1.6)			
Ease of use: Week 24 (n=676)	8.8 (± 1.6)			
Ease of use: Week 48 (n=559)	8.9 (± 1.4)			
Ease of use: Week 72 (n=432)	9.0 (± 1.5)			
Ease of use: Week 96 (n= 353)	9.0 (± 1.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from first injection of IMP up to 2 weeks after last dose of study drug (Week 120).

Adverse event reporting additional description:

Reported AEs were TEAEs that developed or worsened or became serious during the TEAE period (time from the first injection of study drug up to the day of the last injection of study drug + 14 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Alirocumab

Reporting group description:

Subjects received Alirocumab 150 mg SC Q2W or 75 mg SC Q2W added to stable LMT up to a maximum of 120 weeks. Alirocumab dose was either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W, based on Investigator judgment and treatment response.

Serious adverse events	Alirocumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 994 (16.20%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Neoplasm Of Prostate			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder Cancer Stage 0, With Cancer In Situ			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clear Cell Renal Cell Carcinoma			

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon Adenoma				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Tract Adenoma				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Adenocarcinoma				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Myelodysplastic Syndrome				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate Cancer				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Rectal Adenocarcinoma				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional Cell Carcinoma				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine Cancer				

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic Aneurysm				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic Dissection				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep Vein Thrombosis				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intermittent Claudication				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral Arterial Occlusive Disease				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral Artery Aneurysm				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral Artery Stenosis				

subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral Artery Thrombosis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest Discomfort				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest Pain				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac Chest Pain				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular Stent Stenosis				
subjects affected / exposed	4 / 994 (0.40%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Pregnancy Of Partner				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Metrorrhagia				

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatitis				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Epistaxis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Disorder				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Completed Suicide				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Depression				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Product issues			
Device Dislocation			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases Increased			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 994 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip Fracture			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Injury			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Limb Fracture			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus Injury			

subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Peripheral Artery Restenosis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post Procedural Complication				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post Procedural Haematoma				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib Fracture				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Scapula Fracture				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Column Injury				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon Rupture				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Limb Fracture				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular Graft Occlusion				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Accessory Navicular Syndrome				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Coronary Syndrome				
subjects affected / exposed	5 / 994 (0.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Acute Myocardial Infarction				
subjects affected / exposed	5 / 994 (0.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				
subjects affected / exposed	15 / 994 (1.51%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Angina Unstable				
subjects affected / exposed	12 / 994 (1.21%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			

Aortic Valve Stenosis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis Coronary Artery				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	5 / 994 (0.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Tachycardia				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular Block Second Degree				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Disease				

subjects affected / exposed	6 / 994 (0.60%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Stenosis				
subjects affected / exposed	6 / 994 (0.60%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Coronary Ostial Stenosis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral Valve Stenosis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Myocardial Ischaemia				
subjects affected / exposed	5 / 994 (0.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Subendocardial Ischaemia				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular Fibrillation				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amnesia				

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid Artery Stenosis				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Carpal Tunnel Syndrome				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular Accident				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial Paralysis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				

subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	3 / 994 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 994 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 994 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis Ischaemic			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular Perforation			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Diverticulum Intestinal			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia Oral			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perianal Erythema			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal Haemorrhage			

subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical Hernia			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Hepatitis			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular Injury			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertransaminasaemia			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Actinic Keratosis			
subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parapsoriasis			

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Bladder Trabeculation				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal Impairment				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Fibromyalgia				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral Disc Protrusion				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myopathy				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Osteoarthritis				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Polymyalgia Rheumatica				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendonitis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter Colitis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic Foot Infection				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Escherichia Sepsis				

subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Viral				
subjects affected / exposed	2 / 994 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Liver Abscess				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 994 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral Infection				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound Infection				
subjects affected / exposed	1 / 994 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 994 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes Mellitus			
subjects affected / exposed	3 / 994 (0.30%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 994 (0.10%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	221 / 994 (22.23%)		
Nervous system disorders			
Headache			
subjects affected / exposed	61 / 994 (6.14%)		
occurrences (all)	94		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	71 / 994 (7.14%)		
occurrences (all)	93		
Infections and infestations			
Influenza			
subjects affected / exposed	53 / 994 (5.33%)		
occurrences (all)	61		
Nasopharyngitis			
subjects affected / exposed	78 / 994 (7.85%)		
occurrences (all)	86		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2016	Following amendment were made: Reassessment of the number of subjects planned to be enrolled, based on update of the table of expected 95% confidence intervals for various adverse events rates. Streamline of the requirements for the end of study: only one final on-site visit called "End of Treatment/End of Study Visit" (EOT/EOS) was required. Modification in the list of the AE of special interest. Clarification regarding the LDL-C assessment: the Friedewald formula to assess LDL-C was planned to be used even in case TG was elevated (>400 mg/dL). Although there was no formal interim analysis, some statistical analyses might be performed before the end of the study in order to support a dossier of reimbursement if required by health authorities in some countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported