Clinical trial results:
A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients with Elevated Lp(a) (ANITSCHKOW)

Summary

EudraCT number	2015-003731-35
Trial protocol	NL
Global end of trial date	05 April 2018

Results information

Result version number	v1 (current)
This version publication date	14 April 2019
First version publication date	14 April 2019

Trial information

Trial identification

Sponsor protocol code	20130293

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02729025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	05 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of evolocumab on arterial wall inflammation, as measured by percent change from baseline in target-to-background ratio (TBR) of an index vessel by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) at week 16 in subjects with baseline lipoprotein(a) (Lp[a]) ≥ 50 mg/dL and low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, and Food and Drug Administration (FDA) regulations and guidelines set forth in 21 Code of Federal Regulations parts 11, 50, 54, 56, and 312.
The study and all amendments were reviewed by an independent ethics committee (IEC) or institutional review board (IRB).
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 90
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	129
EEA total number of subjects	90

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)	89
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 14 centers in Canada, the Netherlands, and the United States. Participants were enrolled from 14 April 2016 to 07 December 2017.

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to receive either evolocumab or placebo. Randomization was stratified by baseline background statin therapy (on statin versus not on statin) and by screening lipoprotein(a) (Lp(a)) (< 175 mg/dL or ≥ 175 mg/dL).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo to evolocumab by subcutaneous injection once a month (QM) for 12 weeks.

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

Dosage and administration details:

Administered subcutaneously once a month using an autoinjector/pen.

Arm title	Evolocumab 420 mg QM

Arm description:

Participants received 420 mg evolocumab by subcutaneous injection once a month (QM) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Evolocumab
Investigational medicinal product code	AMG 145
Other name	Repatha
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously once a month using an autoinjector/pen.

Number of subjects in period 1	Placebo	Evolocumab 420 mg QM
Started	64	65
Completed	64	64
Not completed	0	1
Sponsor Decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to evolocumab by subcutaneous injection once a month (QM) for 12 weeks.	
Reporting group title	Evolocumab 420 mg QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month (QM) for 12 weeks.	

Reporting group values	Placebo	Evolocumab 420 mg QM	Total
Number of subjects	64	65	129
Age, Customized Units: Subjects			
18 - 64 years	41	48	89
≥ 65 years	23	17	40
Age Continuous Units: years			
arithmetic mean	60.7	60.0	
standard deviation	± 7.6	± 6.8	-
Sex: Female, Male Units: Subjects			
Female	30	39	69
Male	34	26	60
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	2	5
Black or African American	2	4	6
Native Hawaiian or Other Pacific Islander	1	0	1
White	58	58	116
Other	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	64	64	128
Unknown or Not Reported	0	0	0
Location of the Index Vessel Used for Calculation of Maximum Target-to-background Ratio			
The index vessel used to calculate the mean of the maximum target-to-background ratio in the most diseased segment at baseline. Using quantitative fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) image analysis, the artery (right carotid, left carotid, or thoracic aorta) with the highest FDG uptake (highest mean of the maximum target-to-background ratio at baseline) was identified as the index vessel.			
Units: Subjects			
Ascending thoracic aorta	54	49	103
Left common carotid	1	3	4
Right common carotid	8	11	19

Missing	1	2	3
Stratification Factor: Baseline Statin Therapy Units: Subjects			
Yes	33	34	67
No	31	31	62
Stratification Factor: Screening Lipoprotein(a) (Lp[a]) Level Units: Subjects			
< 175 mg/dL	60	61	121
≥ 175 mg/dL	4	4	8
Maximum Target-to-background Ratio (TBR) in the Most Diseased Section in the Index Vessel			
Arterial inflammation was assessed using 18F-fluoro-deoxyglucose positron-emission tomography/computed tomography (FDG PET/CT). Maximum standardized uptake was calculated as time- and dose- corrected tissue radioactivity divided by body weight in the index vessel. TBR was calculated from the ratio of the standardized uptake value of the artery compared to mean background venous activity. Maximum TBR in the most diseased segment was from 3 contiguous slices (approx. 1.5 cm), centered on the slice with the highest maximum TBR in the index vessel. Data were available for 63 subjects in each arm.			
Units: ratio			
arithmetic mean	2.28765	2.29667	
standard deviation	± 0.41284	± 0.46063	-
Lipoprotein(a) Concentration Units: nmol/L			
median	198.0	203.0	
inter-quartile range (Q1-Q3)	151.3 to 300.0	162.5 to 301.5	-
Low-density Lipoprotein Cholesterol (LDL-C) Concentration Units: mg/dL			
arithmetic mean	141.7	146.2	
standard deviation	± 35.7	± 43.5	-
Apolipoprotein B Concentration Units: mg/dL			
arithmetic mean	108.0	109.9	
standard deviation	± 22.9	± 23.7	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo to evolocumab by subcutaneous injection once a month (QM) for 12 weeks.	
Reporting group title	Evolocumab 420 mg QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month (QM) for 12 weeks.	

Primary: Percent Change from Baseline in Maximum Target-to-background Ratio in the Most Diseased Segment of the Index Vessel at Week 16

End point title	Percent Change from Baseline in Maximum Target-to-background Ratio in the Most Diseased Segment of the Index Vessel at Week 16
End point description:	
Arterial inflammation was assessed using 18F-fluoro-deoxyglucose positron-emission tomography/computed tomography (18F-FDG PET/CT). Arterial 18F-FDG uptake is correlated with arterial macrophage content and predicts cardiovascular events. Images were analyzed by an experienced radiologist blinded to all patient characteristics. The maximum standardized uptake value was calculated as a time- and dose- corrected tissue radioactivity divided by body weight in the index and the target-to-background ratio (TBR) was calculated from the ratio of the standardized uptake value of the artery compared to mean background venous activity. The average maximum TBR for the most diseased segment (MDS) was calculated from a group of 3 contiguous slices (approximately 1.5 cm), centered on the slice with the highest maximum TBR in the index vessel. The index vessel was defined as the vessel (either the right or left carotid or aorta) with the highest mean TBR at baseline.	
End point type	Primary
End point timeframe:	
Baseline and week 16	

End point values	Placebo	Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: percent change				
least squares mean (standard error)	-5.31 (± 1.67)	-8.31 (± 1.67)		

Statistical analyses

Statistical analysis title	Treatment Difference
Statistical analysis description:	
A multivariate regression was modelled on the primary endpoint as well as three other response variables (percent change in Lp[a] at Weeks 8 and 16, baseline MDS TBR, and baseline Lp[a]). The primary endpoint was regressed on the treatment group and statin stratification factor; baseline MDS TBR and Lp(a) were regressed on the statin stratification factor, and percent changes in Lp(a) were regressed on the treatment group, statin stratification factor, visit, and treatment group by visit.	
Comparison groups	Placebo v Evolocumab 420 mg QM

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Multivariate regression model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	1.39
Variability estimate	Standard error of the mean
Dispersion value	2.24

Secondary: Percent Change from Baseline in Lipoprotein(a) Concentration at Week 16

End point title	Percent Change from Baseline in Lipoprotein(a) Concentration at Week 16
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and week 16	

End point values	Placebo	Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: percent change				
least squares mean (standard error)	1.06 (± 1.94)	-12.83 (± 1.92)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab 420 mg QM
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-13.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.29
upper limit	-8.49
Variability estimate	Standard error of the mean
Dispersion value	2.73

Notes:

[1] - The model included treatment group, statin stratification, scheduled visit, and the interaction of treatment with scheduled visit.

Secondary: Percent Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C) Concentration at Week 16

End point title	Percent Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C) Concentration at Week 16

End point description:

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Placebo	Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percent change				
least squares mean (standard error)	1.64 (± 1.86)	-59.02 (± 1.82)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab 420 mg QM
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-60.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.81
upper limit	-55.51
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[2] - The model included treatment group, statin stratification, scheduled visit, and the interaction of treatment with scheduled visit.

Secondary: Percent Change from Baseline in Apolipoprotein B Concentration at Week 16

End point title	Percent Change from Baseline in Apolipoprotein B Concentration at Week 16

End point description:

End point type	Secondary

End point timeframe:

Baseline and week 16

End point values	Placebo	Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: percent change				
least squares mean (standard error)	3.29 (± 1.53)	-48.30 (± 1.51)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Evolocumab 420 mg QM
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-51.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.85
upper limit	-47.33
Variability estimate	Standard error of the mean
Dispersion value	2.15

Notes:

[3] - The model included treatment group, statin stratification, scheduled visit, and the interaction of treatment with scheduled visit.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 30 days after the last dose or until the end of study date, whichever was earlier; the maximum duration of treatment was 3.9 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Evolocumab 420 mg QM

Reporting group description:

Participants received 420 mg evolocumab by subcutaneous injection once a month (QM) for 12 weeks.

Reporting group title	Placebo QM

Reporting group description:

Participants received placebo to evolocumab by subcutaneous injection once a month (QM) for 12 weeks.

Serious adverse events	Evolocumab 420 mg QM	Placebo QM	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Evolocumab 420 mg QM	Placebo QM	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 65 (75.38%)	47 / 64 (73.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Dysplastic naevus			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	3 / 65 (4.62%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Peripheral coldness			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Bunion operation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 65 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	5	
Chills			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Drug intolerance			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Fatigue			

subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences (all)	2	2	
Influenza like illness			
subjects affected / exposed	4 / 65 (6.15%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
Injection site hypersensitivity			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Injection site rash			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nodule			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Hypersensitivity			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	

Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Pharyngeal inflammation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	2	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 65 (6.15%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Irritability			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Investigations			
Weight decreased			

subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Bone contusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Epicondylitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Post-traumatic pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Vaccination complication			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			

Dermoid cyst			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Muscular dystrophy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Cervical radiculopathy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	3 / 65 (4.62%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Headache			
subjects affected / exposed	4 / 65 (6.15%)	7 / 64 (10.94%)	
occurrences (all)	5	8	
Hypoaesthesia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Memory impairment			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Paraesthesia			

subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Retinal migraine			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Speech disorder			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Excessive cerumen production			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Abdominal pain lower			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			

subjects affected / exposed	1 / 65 (1.54%)	5 / 64 (7.81%)	
occurrences (all)	1	6	
Dyspepsia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	1 / 65 (1.54%)	5 / 64 (7.81%)	
occurrences (all)	1	5	
Oesophageal pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Peptic ulcer			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Erythema			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

Hyperhidrosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Hyperkeratosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Rash erythematous			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Rosacea			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Arthritis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 65 (1.54%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Bursitis			
subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Lumbar spinal stenosis			

subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	3 / 65 (4.62%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Muscle twitching			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	3 / 65 (4.62%)	2 / 64 (3.13%)	
occurrences (all)	3	2	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	5 / 65 (7.69%)	1 / 64 (1.56%)	
occurrences (all)	5	2	
Osteoarthritis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Rotator cuff syndrome			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 65 (1.54%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Cellulitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

Erysipelas			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
H1N1 influenza			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Heterophyiasis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	7 / 65 (10.77%)	3 / 64 (4.69%)	
occurrences (all)	7	3	
Nail infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	6 / 65 (9.23%)	13 / 64 (20.31%)	
occurrences (all)	6	14	
Otitis externa			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Root canal infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

Upper respiratory tract infection			
subjects affected / exposed	2 / 65 (3.08%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	1 / 65 (1.54%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2016	- The age of the patients included in the study was amended from ≥ 45 to ≥ 50 years to meet the radiation dose limit required by the Dutch ethics committee. - The study schema was updated for clarity. - The primary and exploratory endpoints were reworded for clarity and the methods of analysis for the primary endpoint further detailed.
25 August 2016	- Clarification was provided to minimize the risk of confounding the primary endpoint with prior therapies targeting Lp(a); an exclusion criterion was added to exclude subjects with exposure to therapies targeting Lp(a) within the 12 months prior to screening. - The timing and method of pregnancy testing was clarified. - Additional details regarding the volume of blood drawn to satisfy the existing protocol-specified laboratory testing was included.
08 February 2017	- Blinding of central laboratory test results during the double-blind treatment period was clarified. - Guidance in obtaining local lipid panels was provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported