Clinical trial results:
A Double-blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Summary

EudraCT number	2012-004208-37
Trial protocol	IT NL BE SE CZ HU ES DE GR FI NO IE DK IS
Global end of trial date	29 July 2016

Results information

Result version number	v1 (current)
This version publication date	04 August 2017
First version publication date	04 August 2017

Trial information

Trial identification

Sponsor protocol code	20120153

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01813422
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	29 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated whether low-density lipoprotein (LDL-C) lowering with evolocumab (AMG 145) resulted in greater change from baseline in percent atheroma volume (PAV) at week 78 than placebo in adults with coronary artery disease taking lipid lowering therapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2013
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	Canada: 59
Country: Number of subjects enrolled	United States: 115
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 145
Country: Number of subjects enrolled	Iceland: 7
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Netherlands: 148
Country: Number of subjects enrolled	Norway: 14
Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Russian Federation: 69

Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	South Africa: 45
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	970
EEA total number of subjects	590

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)	661
From 65 to 84 years	308
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 163 centers in 30 countries in Europe, North America, Asia Pacific, and Latin America. The first participant was enrolled on 18 April 2013 and the last participant enrolled on 12 January 2015.

Pre-assignment

Screening details:

Participants who met all entry criteria were randomized 1:1 to receive evolocumab 420 mg once monthly (QM) subcutaneous (SC) or placebo QM SC for 76 weeks. Randomization was stratified by region.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 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 by subcutaneous injection once a month

Arm title	Evolocumab

Arm description:

Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 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:

Evolocumab 420 mg administered by subcutaneous injection once a month

Number of subjects in period 1	Placebo	Evolocumab
Started	486	484
Received Treatment	484	484
Completed	466	468
Not completed	20	16
Adverse event, serious fatal	2	3
Consent withdrawn by subject	14	8
Sponsor Decision	2	1
Lost to follow-up	2	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks.	

Reporting group values	Placebo	Evolocumab	Total
Number of subjects	486	484	970
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	59.8	59.8	
standard deviation	± 8.8	± 9.6	-
Gender, Male/Female Units: Subjects			
Female	135	135	270
Male	351	349	700
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	17	14	31
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	5	4	9
White	453	456	909
Multiple	6	7	13
Other	3	2	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	24	34	58
Not Hispanic or Latino	462	450	912
Unknown or Not Reported	0	0	0
Stratification Factor: Geographical Region Units: Subjects			
North America	88	86	174
Europe	332	332	664
Latin America	16	15	31
Asia Pacific	50	51	101

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks.	

Primary: Change from Baseline in Percent Atheroma Volume at Week 78	
End point title	Change from Baseline in Percent Atheroma Volume at Week 78
End point description:	
Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. The extent of atherosclerosis was expressed as percent atheroma volume (PAV) in a ≥ 40 mm segment of one targeted (imaged) coronary artery, calculated as the percentage of the total vessel volume occupied by atheroma. This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set).	
End point type	Primary
End point timeframe:	
Baseline and week 78	

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	423		
Units: percent atheroma volume				
least squares mean (standard error)	0.053 (± 0.189)	-0.955 (± 0.19)		

Statistical analyses

Statistical analysis title	Primary Analysis of Change from Baseline in PAV
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	846
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS Mean Treatment Difference
Point estimate	-1.007

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.375
upper limit	-0.64
Variability estimate	Standard error of the mean
Dispersion value	0.187

Notes:

[1] - ANCOVA model included terms for the treatment group, the geographic region stratification factor, and baseline PAV.

Secondary: Change from Baseline in Total Atheroma Volume at Week 78

End point title	Change from Baseline in Total Atheroma Volume at Week 78

End point description:

Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. Total atheroma volume (TAV) in a ≥ 40 mm segment of the targeted coronary artery was calculated as the average plaque area over the number of images that were evaluated by IVUS multiplied by the median vessel length to compensate for differences in segment length between participants.
This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set).

End point type	Secondary

End point timeframe:

Baseline and week 78

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	423		
Units: mm^3				
least squares mean (standard error)	-0.91 (± 1.214)	-5.799 (± 1.216)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in TAV
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	846
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS Mean Treatment Difference
Point estimate	-4.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.247
upper limit	-2.531

Variability estimate	Standard error of the mean
Dispersion value	1.201

Notes:

[2] - ANCOVA model included terms for the treatment group, the geographic region stratification factor, and baseline TAV.

Secondary: Percentage of Participants with Regression in Percent Atheroma Volume

End point title	Percentage of Participants with Regression in Percent Atheroma Volume

End point description:

Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. The extent of atherosclerosis was expressed as percent atheroma volume (PAV) in a ≥ 40 mm segment of one targeted (imaged) coronary artery, calculated as the percentage of the total vessel volume occupied by atheroma. Regression in PAV was defined as any reduction from baseline in PAV.
This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set)

End point type	Secondary

End point timeframe:

Baseline and week 78

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	423		
Units: percentage of participants				
number (confidence interval 95%)	47.3 (42.6 to 52)	64.3 (59.6 to 68.7)		

Statistical analyses

Statistical analysis title	Analysis of Regression in PAV
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	846
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	17
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.3
upper limit	23.5

Notes:

[3] - Based on CMH test stratified by geographic region.

Secondary: Percentage of Participants with Regression in Total Atheroma Volume

End point title	Percentage of Participants with Regression in Total Atheroma Volume

End point description:

Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. Total atheroma volume (TAV) in a ≥ 40 mm segment of the targeted coronary artery was calculated as the average plaque area over the number of images that were evaluated by IVUS multiplied by the median vessel length to compensate for differences in segment length between participants. Regression in TAV was defined as any reduction from baseline in TAV.
This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set).

End point type	Secondary

End point timeframe:

Baseline and week 78

End point values	Placebo	Evolocumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	423		
Units: percentage of participants				
number (confidence interval 95%)	48.9 (44.2 to 53.7)	61.5 (56.7 to 66)		

Statistical analyses

Statistical analysis title	Analysis of Regression in TAV
Comparison groups	Placebo v Evolocumab
Number of subjects included in analysis	846
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.8
upper limit	19.1

Notes:

[4] - Based on CMH test stratified by geographic region.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until week 80	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks.	
Reporting group title	Evolocumab
Reporting group description:	
Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks.	

Serious adverse events	Placebo	Evolocumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	142 / 484 (29.34%)	135 / 484 (27.89%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma of skin			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign pancreatic neoplasm			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer stage I, with cancer in situ			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemodectoma			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage III			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral neoplasm			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	4 / 484 (0.83%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 484 (0.00%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 484 (0.41%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raynaud's phenomenon			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoconstriction			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel perforation			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary revascularisation			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	6 / 484 (1.24%)	11 / 484 (2.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site haemorrhage			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent restenosis			
subjects affected / exposed	2 / 484 (0.41%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent stenosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 484 (0.21%)	4 / 484 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 484 (0.21%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 484 (0.21%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 484 (0.21%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram coronary			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural dizziness			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 484 (0.62%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 484 (1.03%)	6 / 484 (1.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	11 / 484 (2.27%)	17 / 484 (3.51%)	
occurrences causally related to treatment / all	0 / 12	2 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	7 / 484 (1.45%)	8 / 484 (1.65%)	
occurrences causally related to treatment / all	1 / 7	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	5 / 484 (1.03%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 484 (0.83%)	6 / 484 (1.24%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	13 / 484 (2.69%)	7 / 484 (1.45%)	
occurrences causally related to treatment / all	0 / 13	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery dissection			
subjects affected / exposed	2 / 484 (0.41%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 484 (0.21%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	5 / 484 (1.03%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	4 / 484 (0.83%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	3 / 484 (0.62%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 484 (0.21%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 484 (0.21%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cataract			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder enlargement			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder prolapse			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 484 (0.00%)	3 / 484 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 484 (0.41%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 484 (0.62%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 484 (0.21%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 484 (0.21%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 484 (0.83%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective staphylococcal			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection toxoplasmal			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 484 (1.03%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 484 (0.00%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 484 (0.21%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	2 / 484 (0.41%)	2 / 484 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 484 (0.00%)	1 / 484 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	1 / 484 (0.21%)	0 / 484 (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: 5 %

Non-serious adverse events	Placebo	Evolocumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 484 (24.79%)	114 / 484 (23.55%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	34 / 484 (7.02%)	29 / 484 (5.99%)	
occurrences (all)	36	32	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	32 / 484 (6.61%)	21 / 484 (4.34%)	
occurrences (all)	37	24	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 484 (5.99%)	19 / 484 (3.93%)	
occurrences (all)	34	21	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	26 / 484 (5.37%)	33 / 484 (6.82%)	
occurrences (all)	31	35	
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	27 / 484 (5.58%) 31	34 / 484 (7.02%) 39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2013	Major changes included: •added known hemorrhagic stroke and personal or family history of hereditary muscular disorders to exclusion criteria •added clarification to the criteria for the target coronary artery for IVUS •added an alert threshold for elevated triglycerides •updated the criteria for withholding investigational product to include criteria for withholding atorvastatin •updated the serious adverse event reporting window •updated the prohibited treatments section •implemented minor clarifications and error corrections
20 December 2013	Major changes included: •modified inclusion criteria to allow additional statins beyond atorvastatin (simvastatin, rosuvastatin, pravastatin, lovastatin, and pitastatin); statin intolerant subjects (limit up to 10%); niacin and ezetimibe background therapy, provided it was stable for 4 weeks prior to screening •added inclusion criteria that subjects had be on a stable, optimized background therapy and on an effective statin dose of at least atorvastatin 20mg daily or equivalent •added exclusion of subjects on mipomersen or lomitapide in the last 12 months prior to LDL-C screening •clarified definition of regression by PAV and TAV for secondary endpoints •updated safety sections per the new Amgen template •changed dosing nomenclature from Q4W to QM •added device language to allow subjects to use the 3.5 mL personal injector when available •implemented other clarifications to inclusion/exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported