Clinical trial results:
Effects of ivabradine on plaque burden, morphology and composition in patients with clinically indicated coronary angiography. A randomised double-blind placebo-controlled international multicentre study.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-004779-38
Trial protocol	FI GB ES PT SK BE DE CZ HU PL SE NO DK GR FR
Global end of trial date	10 September 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	06 July 2016

Trial information

Trial identification

Sponsor protocol code	CL3-16257-102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France,
Public contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.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	10 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2014
Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ivabradine treatment for 18 months on atherosclerotic disease progression as assessed using coronary Intravascular Ultrasound (IVUS) in patients with coronary artery disease (CAD).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.
Care was taken to ensure that the plaque burden in the target artery was not too high as to significantly increase the risk incurred by the imaging procedures.

The decision to prematurely discontinue the study (issued in agreement with the Study Executive Committee and the Data Monitoring Committee) was triggered by the results of the SIGNIFY study which used the same therapeutic schemas as the present study (up-titration up to 10 mg bid) and failed to demonstrate the efficacy of ivabradine in preventing cardiovascular events in patients with CAD and without clinical heart failure.

Background therapy:

Treatment with optimal doses of lipid lowering therapies and recommended treatment for CAD.

Evidence for comparator: -

Actual start date of recruitment	24 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	Poland: 64
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Australia: 16

Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Taiwan: 26
Worldwide total number of subjects	360
EEA total number of subjects	197

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)	251
From 65 to 84 years	108
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were male or female (non-childbearing potential) aged 18 years or older, in sinus rhythm and HR ≥ 70 bpm, with coronary artery disease who had a clinical indication for coronary angiography.

Pre-assignment

Screening details:

Patients had to show a sufficient level of atheroma burden (at least one stenosis > 20%) or a prior history of percutaneous coronary intervention without increasing significantly the risk incurred by intravascular ultrasound or optical coherence tomography procedures (no stenosis > 50% in the target artery).

Period 1

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

Blinding implementation details:

Identical tablets and packaging for the two treatment arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine

Arm description:

18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.

Arm type	Experimental
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	16257
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In patients < 75 years, starting dose was 7.5 mg twice daily then maintained at 7.5 mg or up-titrated to 10 mg or down-titrated to 5 mg. In elderly patients (≥ 75 years), starting dose was 5 mg twice daily with possibly up-titration to 7.5 mg and then 10 mg.

Arm title	placebo

Arm description:

18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets matching those of ivabradine with the same titration protocol as described in the ivabradine arm.

Number of subjects in period 1	Ivabradine	placebo
Started	178	182
Completed	0	0
Not completed	178	182
Consent withdrawn by subject	8	5
Adverse event, non-fatal	3	-
premature study termination	167	177

Baseline characteristics

Reporting groups	
Reporting group title	Ivabradine
Reporting group description:	
18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.	
Reporting group title	placebo
Reporting group description:	
18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.	

Reporting group values	Ivabradine	placebo	Total
Number of subjects	178	182	360
Age categorical Units: Subjects			
Adults (18-64 years)	132	119	251
From 65-84 years	45	63	108
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	59.4	59.8	
standard deviation	± 8.9	± 9.7	-
Gender categorical Units: Subjects			
Female	50	55	105
Male	128	127	255

End points

End points reporting groups

Reporting group title	Ivabradine
Reporting group description:	
18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.	
Reporting group title	placebo
Reporting group description:	
18 months of treatment with visits at 1, 2, 3, 6, 9, 12, 15, 18 months and a second IVUS at 18 months.	
Subject analysis set title	Randomised Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All included and randomised patients	

Primary: Coronary Percent Atheroma Volume

End point title	Coronary Percent Atheroma Volume[1]
End point description:	
Following the premature termination of the study, the post-baseline coronary imaging measurements were not performed.	
End point type	Primary
End point timeframe:	
Change in coronary Percent Atheroma Volume from baseline to the study end for all anatomically comparable slices in a 30-mm segment of the target coronary artery.	

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: Post-baseline primary endpoint was not assessed. No statistical analysis was performed.

End point values	Ivabradine	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: not available				

Notes:

[2] - post-baseline primary endpoint not assessed

[3] - post-baseline primary endpoint not assessed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred during the treatment period are presented here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	placebo
Reporting group description: -	
Reporting group title	Ivabradine

Reporting group description: -

Serious adverse events	placebo	Ivabradine	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 181 (13.81%)	22 / 176 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 181 (1.10%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal hernia repair			

subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm repair			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac rehabilitation therapy			
subjects affected / exposed	2 / 181 (1.10%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary revascularisation			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			
subjects affected / exposed	3 / 181 (1.66%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery angioplasty			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Metaplasia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			

Activities of daily living impaired			
subjects affected / exposed	1 / 181 (0.55%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired driving ability			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (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	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 181 (0.55%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bradycardia			
subjects affected / exposed	0 / 181 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 181 (0.55%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (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	1 / 181 (0.55%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral artery stenosis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photopsia			
subjects affected / exposed	1 / 181 (0.55%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy proliferative			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vision blurred			
subjects affected / exposed	1 / 181 (0.55%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic congestion			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (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			
Renal failure chronic			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			

subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (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			
Pneumonia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 181 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 181 (0.55%)	0 / 176 (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: 1 %

Non-serious adverse events	placebo	Ivabradine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 181 (36.46%)	80 / 176 (45.45%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 181 (2.21%)	3 / 176 (1.70%)	
occurrences (all)	4	3	

Aspartate aminotransferase increased			
subjects affected / exposed	3 / 181 (1.66%)	2 / 176 (1.14%)	
occurrences (all)	3	2	
Blood cholesterol increased			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Blood triglycerides increased			
subjects affected / exposed	1 / 181 (0.55%)	3 / 176 (1.70%)	
occurrences (all)	1	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 181 (1.66%)	3 / 176 (1.70%)	
occurrences (all)	3	3	
Heart rate decreased			
subjects affected / exposed	1 / 181 (0.55%)	9 / 176 (5.11%)	
occurrences (all)	1	10	
High density lipoprotein decreased			
subjects affected / exposed	0 / 181 (0.00%)	3 / 176 (1.70%)	
occurrences (all)	0	3	
Low density lipoprotein increased			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 181 (2.21%)	9 / 176 (5.11%)	
occurrences (all)	4	10	
Hypotension			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Orthostatic hypotension			
subjects affected / exposed	4 / 181 (2.21%)	1 / 176 (0.57%)	
occurrences (all)	4	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Bradycardia			

subjects affected / exposed	1 / 181 (0.55%)	3 / 176 (1.70%)	
occurrences (all)	1	3	
Bundle branch block right			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences (all)	2	0	
Sinus bradycardia			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Sinus tachycardia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences (all)	2	0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Ventricular extrasystoles			
subjects affected / exposed	1 / 181 (0.55%)	4 / 176 (2.27%)	
occurrences (all)	1	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 181 (3.31%)	3 / 176 (1.70%)	
occurrences (all)	6	4	
Dizziness postural			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	3 / 181 (1.66%)	3 / 176 (1.70%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 181 (0.55%)	5 / 176 (2.84%)	
occurrences (all)	1	5	
Chest pain			
subjects affected / exposed	4 / 181 (2.21%)	3 / 176 (1.70%)	
occurrences (all)	4	3	
Local swelling			

subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences (all)	2	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 181 (0.55%)	2 / 176 (1.14%)	
occurrences (all)	1	3	
Oedema peripheral			
subjects affected / exposed	2 / 181 (1.10%)	4 / 176 (2.27%)	
occurrences (all)	2	4	
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 181 (0.00%)	13 / 176 (7.39%)	
occurrences (all)	0	14	
Vision blurred			
subjects affected / exposed	2 / 181 (1.10%)	8 / 176 (4.55%)	
occurrences (all)	2	9	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 181 (0.00%)	3 / 176 (1.70%)	
occurrences (all)	0	4	
Constipation			
subjects affected / exposed	3 / 181 (1.66%)	2 / 176 (1.14%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	2 / 181 (1.10%)	1 / 176 (0.57%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 181 (1.10%)	2 / 176 (1.14%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 181 (2.21%)	0 / 176 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	1 / 181 (0.55%)	4 / 176 (2.27%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Pruritus generalised			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 181 (0.55%)	2 / 176 (1.14%)	
occurrences (all)	1	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	0 / 181 (0.00%)	2 / 176 (1.14%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	6 / 181 (3.31%)	4 / 176 (2.27%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 181 (1.10%)	0 / 176 (0.00%)	
occurrences (all)	2	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 181 (0.00%)	3 / 176 (1.70%)	
occurrences (all)	0	3	
Type 2 diabetes mellitus			

subjects affected / exposed occurrences (all)	2 / 181 (1.10%) 2	1 / 176 (0.57%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2013	The following points were added: treatment with strong cytochrome P450 3A4 inhibitor as non-inclusion criteria, a centralised analysis of the blood samples for lipid profile, -an optional genomic analysis. The assessment of biomarkers pertinent to the atherosclerotic process was updated.
04 December 2013	A Data Monitoring Committee (DMC) was constituted. History of persistent atrial fibrillation was added as non-selection criteria. During the coronary angiography procedure for entry in the study, the use of 3-lead ECG (if no 12-lead ECG available) as well as the use -of an equivalent treatment to nitroglycerin were authorised. -

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The median treatment duration was 4.5 months with a maximum of 13.5 months. Thus, the M18 visit (and second IVUS examination) was not attained by any patient, so no estimation of treatment effect on the primary criterion was possible.

Notes: