



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

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

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

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