



Clinical trial results:

Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered orally at the therapeutic doses (2.5/5/7.5 mg b.i.d.) on top of anti-anginal background therapy, to patients with chronic stable angina pectoris.

An international, double-blind placebo controlled 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 | 2006-005475-17 |
| Trial protocol | IE PT BE FI GB HU SE DE |
| Global end of trial date | 12 February 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 02 March 2016 |
| First version publication date | 02 March 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CL3-16257-067 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN99185656 |
| 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 1 55 72 43 66, clinicaltrials@servier.com |
| Scientific contact | ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 1 55 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 | 12 February 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 February 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To document the absence of retinal toxicity of ivabradine versus placebo in chronic stable angina patients after treatment cessation in the subset of patients with emergent bilateral relevant ERG abnormalities observed at 36 months under treatment. Consequently, the main endpoint of the study was a safety endpoint.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in Seoul 2008.

Mandatory withdrawal from the study if study drug not tolerated, prolonged loss of sinus rhythm, occurrence of condition preventing the assessment of visual function or morphology, condition or treatment of the visual system which irreversibly reduced visual function beyond that reasonably attributable to age and/or established underlying condition such as diabetes, pregnancy.

Other criteria for premature withdrawal of the study: adverse event requiring discontinuation of study drug and/or administration of an unauthorized concomitant treatment.

Background therapy:

Standard anti-anginal therapies.

Evidence for comparator:

Not applicable

| | |
|---|---------------|
| Actual start date of recruitment | 29 April 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Portugal: 16 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Australia: 15 |
| Country: Number of subjects enrolled | Singapore: 3 |
| Country: Number of subjects enrolled | Argentina: 28 |

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 97 |
| EEA total number of subjects | 51 |

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) | 45 |
| From 65 to 84 years | 52 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study population was male or female with chronic stable angina pectoris, with reliable baseline electroretinogram and visual fields (static and kinetic), in stable condition regarding the angina symptoms and related treatments, in sinus rhythm and with a resting HR \geq 60 bpm.

Period 1

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

Blinding implementation details:

Treatment randomisation and allocation centralized (interactive system response).

Study products of identical appearance.

Arms

| | |
|--|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ivabradine |
| Arm description: - | |
| Arm type | test drug |
| Investigational medicinal product name | Ivabradine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Starting dose of 5 mg twice daily or 2.5 mg twice daily (patients > 75 years and/or with concomitant treatment with moderate CYP3A4 inhibitors). During this period, highest dose was 7.5 mg twice daily and lowest dose 2.5 mg twice daily.

| | |
|--|----------|
| Arm title | Placebo |
| Arm description: - | |
| 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:

One placebo tablet (matching ivabradine tablet) twice daily.

| Number of subjects in period 1 | Ivabradine | Placebo |
|--------------------------------|------------|---------|
| Started | 50 | 47 |
| Completed | 39 | 37 |
| Not completed | 11 | 10 |
| Adverse event, serious fatal | 1 | 1 |
| Consent withdrawn by subject | 5 | 4 |
| Adverse event, non-fatal | 5 | 4 |
| Lost to follow-up | - | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Run-out |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

| | |
|--|----------|
| 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:

One placebo tablet (matching ivabradine tablet) twice daily.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

| | |
|--|----------|
| 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:

One placebo tablet (matching ivabradine tablet) twice daily.

| Number of subjects in period 2 | Placebo | Placebo |
|---------------------------------------|---------|---------|
| Started | 39 | 37 |
| Completed | 39 | 37 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Ivabradine |
|-----------------------|------------|

| |
|--------------------------------|
| Reporting group description: - |
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| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values | Ivabradine | Placebo | Total |
|------------------------|------------|---------|-------|
| Number of subjects | 50 | 47 | 97 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 24 | 21 | 45 |
| From 65-84 years | 26 | 26 | 52 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.4 | 63.6 | |
| standard deviation | ± 7.8 | ± 8.2 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 19 | 40 |
| Male | 29 | 28 | 57 |

End points

End points reporting groups

| | |
|--|---------------------------|
| Reporting group title | Ivabradine |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: | |
| All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo. | |
| Subject analysis set title | Sub-Safety Ophthalmic Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| For the ophthalmic (OPH) safety analyses, a Safety Ophthalmic Set (SOS) was defined as all patients having received at least one dose of study drug and with at least one evaluation from at least one reliable OPH test (ERG, visual field ...) for each eye at baseline and at M36 (after 3-years of treatment) under treatment or at M38 (i.e. two months after treatment cessation). The SSOS was defined as all patients of the SOS with a bilateral relevant ERG abnormality at M36 under treatment on at least one of the four main ERG criteria (composite endpoint) and a reliable ERG test at M36 under treatment for each eye and at M38. | |

Primary: Bilateral relevant ERG abnormality

| | |
|--|------------------------------------|
| End point title | Bilateral relevant ERG abnormality |
| End point description: | |
| Four main ERG criteria were defined as following: | |
| Standard combined rod/cone response (3RC) a- and b-waves, amplitude. | |
| -Standard combined rod/cone response (3RC) a- and b-waves, implicit time. | |
| Single flash cone response (SFC) a- and b-waves, amplitude. | |
| Single flash cone response (SFC) a- and b-waves, implicit time. | |
| End point type | Primary |
| End point timeframe: | |
| In patients with at least one bilateral relevant abnormality at M36 under treatment (SSOS, N = 5), presence (yes/no) of a bilateral relevant abnormality at M38 on at least one of the four main ERG criteria. | |

| End point values | Ivabradine | Placebo | Sub-Safety Ophthalmic Set | |
|-----------------------------|------------------|------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 2 ^[1] | 3 ^[2] | 5 | |
| Units: number of patients | 0 | 1 | 1 | |

Notes:

[1] - Both patients had a single ERG response affected at M36.

[2] - Each of these 3 patients had several ERG responses/components affected at M36.

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Primary composite safety endpoint |
| Statistical analysis description: | |
| Estimate of the difference between the two groups was given using 95% CI based on the Wilson score method . | |
| Comparison groups | Ivabradine v Placebo |
| Number of subjects included in analysis | 5 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -33.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -87.69 |
| upper limit | 52.87 |

Notes:

[3] - To estimate the difference between ivabradine and placebo on an incidence rate (bilateral relevant ERG abnormality after treatment cessation at M36) using a non-parametric approach.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported all over the study. Adverse events reported over the 3-year double-blind treatment period in patients who received at least one dose of study drug are presented here as it was the only period when patients received ivabradine.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Ivabradine |
|-----------------------|------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Ivabradine | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 50 (42.00%) | 19 / 47 (40.43%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial stromal sarcoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemodynamic instability | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (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 | | | |
| Gastric banding | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| 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 pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|----------------|----------------|--|
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (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 | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (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 | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematuria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (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 unstable | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 6 / 47 (12.77%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 2 / 47 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bundle branch block right | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sick sinus syndrome | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus arrest | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| syncope | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| 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 | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------------------------|----------------------------------|--|
| Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 50 (4.00%) 0 / 2 0 / 0 | 1 / 47 (2.13%) 0 / 1 0 / 0 | |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 50 (2.00%) 0 / 1 0 / 0 | 1 / 47 (2.13%) 0 / 1 0 / 0 | |
| Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 50 (2.00%) 0 / 1 0 / 0 | 0 / 47 (0.00%) 0 / 0 0 / 0 | |
| Bacterial infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 50 (2.00%) 0 / 1 0 / 0 | 0 / 47 (0.00%) 0 / 0 0 / 0 | |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 50 (2.00%) 0 / 1 0 / 0 | 0 / 47 (0.00%) 0 / 0 0 / 0 | |
| Gastroenteritis salmonella subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 50 (2.00%) 0 / 1 0 / 0 | 0 / 47 (0.00%) 0 / 0 0 / 0 | |
| Herpes simplex encephalitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 50 (0.00%) 0 / 0 0 / 0 | 1 / 47 (2.13%) 0 / 1 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 50 (0.00%) 0 / 0 0 / 0 | 1 / 47 (2.13%) 0 / 1 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Septic shock | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ophthalmic herpes zoster | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 47 (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: 4 %

| Non-serious adverse events | Ivabradine | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 50 (80.00%) | 37 / 47 (78.72%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 50 (12.00%) | 9 / 47 (19.15%) | |
| occurrences (all) | 7 | 10 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 2 | 2 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 2 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 0 | 2 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 1 | 3 | |
| Depression | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 0 | 3 | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Investigations | | | |
| Heart rate decreased | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 5 | 2 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 2 | 4 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 2 | 4 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 6 / 50 (12.00%) | 6 / 47 (12.77%) | |
| occurrences (all) | 6 | 7 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 2 | 3 | |
| Cardiac failure | | | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 3 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 5 | 3 | |
| Headache | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 3 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 6 / 50 (12.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 7 | 3 | |
| Cataract nuclear | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Photopsia | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 4 | 2 | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 0 | 2 | |
| Blepharitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 2 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 3 | 2 | |
| Eyelid disorder | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Gastroesophageal reflux disease subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 1 / 47 (2.13%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 47 (0.00%) 0 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 47 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 2 / 47 (4.26%) 2 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 47 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 4 / 47 (8.51%) 4 | |
| Myalgia subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 47 (0.00%) 0 | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 2 / 47 (4.26%) 2 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 47 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 7 | 3 / 47 (6.38%) 3 | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 1 / 47 (2.13%) 1 | |

| | | | |
|-------------------------------------|----------------|----------------|--|
| Sinusitis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 1 | 3 | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 2 | 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 3 / 47 (6.38%) | |
| occurrences (all) | 0 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 47 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 2 | 2 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 2 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 July 2009 | Extension of study completion date. Non-selection criteria: patients currently or having treated with not marketed (added) ivabradine. Time window between the last visit of double-blind treatment period and the visit of run-out period: 1 to 3 months allowed. Cyclosporine removed from unauthorised concomitant treatments. |
| 23 December 2009 | Extension of study completion date. |
| 27 April 2012 | Number of planned patients reduced from 300 to 100. Extension of study completion date. |
| 10 September 2012 | To comply with changes of the Summary of Products Characteristics for ivabradine product. Final threshold values for potential clinical concern related to the ERG responses were calculated taking in account the data of patients included in the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported