



Clinical trial results:

Effects of oral chronic administration of ivabradine (7.5 mg b.i.d.) in comparison to placebo (b.i.d.) on top of beta-blockers, on central aortic blood pressure. Randomised, cross-over, double-blind, multicentre, study over 10 weeks in patients with stable coronary artery disease and a resting heart rate equal or superior to 70 bpm, already treated with beta-blockers.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-004779-35 |
| Trial protocol | IE IT |
| Global end of trial date | 13 May 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2016 |
| First version publication date | 31 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CL2-16257-096 |
|-----------------------|---------------|

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, 92284 |
| Public contact | Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com |
| Scientific contact | Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155724366, 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 | 13 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 May 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of ivabradine on central aortic systolic blood pressure (CASBP) in comparison to placebo in patients with stable coronary artery disease (CAD), and a resting heart rate (HR) \geq 70 bpm, treated by beta-blockers (BBs).

Protection of trial subjects:

Non-selection criteria:

- Pregnant women, breast-feeding or women of childbearing potential not using, oestro-progestative or progestative or intra-uterine contraception or subcutaneous contraceptive implant, or using oestro-progestative or progestative or intra-uterine contraception or subcutaneous contraceptive implant but who consider stopping it during the duration of the study
- History of central neuropathy and/or of symptomatic orthostatic hypotension of nonmedicamentous etiology
- Severe hypotension at the time of selection (blood pressure < 90 / 50 mmHg)
- Patient currently or previously treated with ivabradine within the last 3 months before selection visit
- Patient currently or previously treated with nebivolol within the last 3 months before selection visit
- Patients with recent (less than 3 months) MI or coronary revascularisation
- Patients with recent (less than 3 months) stroke or cerebral transient ischemic attack
- Patients scheduled for coronary revascularisation procedures
- Patients with transplanted heart
- Implanted pacemaker, implantable cardioverter defibrillator, cardiac resynchronisation therapy
- Valvular disease likely to require surgery within the coming year
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome, sino-atrial block, congenital long QT, 2nd degree and complete atrio-ventricular block
- Patients with angina at rest and angina of class IV
- Clinical signs and/or symptoms of heart failure in NYHA class II or higher
- Hospitalisation for heart failure as primary diagnosis within the last 12 months
- Known carriers of hepatitis B surface antigen or human immunodeficiency virus antibodies or hepatitis C virus antibodies
- Known alcohol or drug abuse
- Patients requiring treatments which are not allowed during the study
- Known hypersensitivity or contra-indication to the administration of ivabradine
- Known hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Background therapy:

Beta-blockers at doses estimated appropriate by the investigators.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 05 June 2012 |
| 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 | Ireland: 3 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Italy: 1 |
| Worldwide total number of subjects | 14 |
| EEA total number of subjects | 14 |

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) | 9 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Males and females (at least 30 years old) with medical history of CAD, with sinus rhythm, stable and appropriate treatment by beta blockers at the exception of nebivolol and carvedilol, with sinus rhythm and 12-lead ECG HR \geq 70 bpm at selection and at inclusion visit, with normal fasting laboratory results and informed consent obtained.

Period 1

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

Arms

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

Arm description:

- 3-week double-blind active treatment period P1: patients received Ivabradine
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Placebo

| | |
|--|------------|
| Arm type | Test drug |
| Investigational medicinal product name | Ivabradine |
| Investigational medicinal product code | S16257 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

7.5 mg tablets twice a day at 12-hour intervals during meals, at breakfast and dinner, starting the next morning at breakfast after the visit.

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matched tablets twice a day during meals, at breakfast and at dinner, starting the next morning after the visit.

| | |
|------------------|--------------------|
| Arm title | Placebo/Ivabradine |
|------------------|--------------------|

Arm description:

- 3-week double-blind active treatment period P1: patients received Placebo
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Ivabradine

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

Matched tablets twice a day during meals, at breakfast and at dinner, starting the next morning after the visit.

| | |
|--|------------|
| Investigational medicinal product name | Ivabradine |
| Investigational medicinal product code | S16257 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

7.5 mg tablets twice a day at 12-hour intervals during meals, at breakfast and dinner, starting the next morning at breakfast after the visit.

| Number of subjects in period 1 | Ivabradine/Placebo | Placebo/Ivabradine |
|---------------------------------------|--------------------|--------------------|
| Started | 6 | 8 |
| Completed | 6 | 6 |
| Not completed | 0 | 2 |
| Adverse event, non-fatal | - | 1 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Ivabradine/Placebo |
|-----------------------|--------------------|

Reporting group description:

- 3-week double-blind active treatment period P1: patients received Ivabradine
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Placebo

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Ivabradine |
|-----------------------|--------------------|

Reporting group description:

- 3-week double-blind active treatment period P1: patients received Placebo
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Ivabradine

| Reporting group values | Ivabradine/Placebo | Placebo/Ivabradine | Total |
|--|--------------------|--------------------|-------|
| Number of subjects | 6 | 8 | 14 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 2 | 7 | 9 |
| From 65-84 years | 4 | 1 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 69 | 58.4 | |
| standard deviation | ± 7.8 | ± 5.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 1 | 2 |
| Male | 5 | 7 | 12 |

End points

End points reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Ivabradine/Placebo |
|-----------------------|--------------------|

Reporting group description:

- 3-week double-blind active treatment period P1: patients received Ivabradine
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Placebo

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Ivabradine |
|-----------------------|--------------------|

Reporting group description:

- 3-week double-blind active treatment period P1: patients received Placebo
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Ivabradine

| | |
|----------------------------|------------|
| Subject analysis set title | Ivabradine |
|----------------------------|------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The Per Protocol Set (PPS) consisted of 9 patients

| | |
|----------------------------|---------|
| Subject analysis set title | Placebo |
|----------------------------|---------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The Per Protocol Set (PPS) consisted of 9 patients

Primary: CASBP-change from baseline over 3-week treatment period

| | |
|-----------------|--|
| End point title | CASBP-change from baseline over 3-week treatment period ^[1] |
|-----------------|--|

End point description:

Change of central aortic systolic blood pressure from baseline.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Change from baseline over 3-week treatment period

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: Due to recruitment issues, the study was prematurely stopped after 14 patients were included. Therefore only descriptive statistics will be performed.

| End point values | Ivabradine | Placebo | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 9 | 9 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -3.3 (\pm 10.2) | 1 (\pm 9.4) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE occurring during treatment periods only.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

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 | 0 / 12 (0.00%) | 1 / 14 (7.14%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 14 (7.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Ivabradine | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 2 / 14 (14.29%) | |
| Injury, poisoning and procedural complications | | | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |

| | | | |
|--|---|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 14 (0.00%) 0 | |
| Eye disorders Photopsia subjects affected / exposed occurrences (all) Retinal disorder subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 4 1 / 12 (8.33%) 1 | 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 14 (7.14%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 14 September 2012 | This amendment will apply to the centers in FRANCE, IRELAND and ITALY: <ul style="list-style-type: none">- Precision on CAD and Type II diabetes documentation.- Addition of carvedilol to not allowed previous beta-blocker treatment. Addition of substance-induced long QT as medical and therapeutic non-selection criterion.- Addition of carvedilol to not allowed previous beta-blocker treatments.- Addition of potassium-depleting diuretics as treatment to be used with precautions in patients receiving ivabradine and having long QT interval. Addition of carvedilol and marketed ivabradine to not allowed concomitant treatments.- Precision on tonometry methods (dominant arm)- Precision on blood pressure measurement (dominant arm)- Update the list of adverse events for which specific information is requested and already collected. |
| 26 March 2013 | This amendment will apply to the centers in FRANCE, IRELAND and ITALY: The main changes are: <ul style="list-style-type: none">- The removal of the type II diabetes selection criteria.- The change of the planned date of Last Visit Last Patient- The addition of a non-inclusion criterion related to the quality of applanation tonometry at inclusion visit. |
| 03 July 2013 | This amendment will apply to the centers in FRANCE, IRELAND and ITALY: The main changes are: <ul style="list-style-type: none">- The addition of a new participating Country/Centre in Italy and the possibility to set-up a new centre, not yet identified, in France- The modification of titles of sponsor signatories- The measurement of skin capillary density only in patients from centres equipped with the adequate material- The addition of non-selection and non-inclusion criteria related to the type and to the stability of diabetes before selection. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-------------|---|--------------|
| 13 May 2014 | The study was prematurely stopped due to recruitment issue. | - |

Notes:

Limitations and caveats

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

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report;

Notes: