



## Clinical trial results:

**Effects of oral administration of ivabradine (7.5 mg bid) on post-ischaemic stunning induced by exercise stress in patients with coronary artery disease and exercise inducible ischaemia.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000783-98 |
| Trial protocol           | IT             |
| Global end of trial date | 13 August 2014 |

### Results information

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

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL2-16257-095 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN90566768 |
| 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               | Innovation Therapeutic Pole, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com |
| Scientific contact           | Innovation Therapeutic 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:

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**Results analysis stage**

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|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 13 August 2014 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 13 August 2014 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the effects of Ivabradine on post-ischaemic stunning induced by exercise stress in patients with stable coronary artery disease and exercise-inducible ischaemia

Protection of trial subjects:

The study treatment could be prematurely discontinued if it was not tolerated, no longer appropriate or considered as contra-indicated.

For the sake of safety, only patients presenting with a positive exercise at moderate or high workload were selected in the study, thus patients with low-effort inducible ischemia were not included.

Background therapy:

Previous cardiovascular medication were maintained except previous anti-angina treatments. Short acting nitrates were authorized during the study.

Evidence for comparator:

Not applicable

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 27 March 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 15 |
| Worldwide total number of subjects   | 15        |
| EEA total number of subjects         | 15        |

Notes:

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**Subjects enrolled per age group**

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|                                           |   |
|-------------------------------------------|---|
| 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)                      | 5 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 10 |
| 85 years and over   | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was carried out under the supervision of Prof. P.G. Camici in a unique centre at Istituto Scientifico Universitario San Raffaele, Milan, Italy

### Pre-assignment

Screening details:

Study population was male and female patients with proven Coronary Artery Disease, Left Ventricular Ejection Fraction  $\geq 40\%$ , sinus rhythm, resting heart rate  $\geq 70$  bpm and exercise-inducible myocardial ischaemia at moderate to high workload and subsequent stunning. 26 patients were screened; 25 patients pre-selected and 15 patients were included.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 26 <sup>[1]</sup> |
| Number of subjects completed | 15                |

### Pre-assignment subject non-completion reasons

|                            |                                          |
|----------------------------|------------------------------------------|
| Reason: Number of subjects | non compliance to selection criteria: 11 |
|----------------------------|------------------------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 11 patients showed non-compliance to selection criteria

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Ivabradine (overall period) |
| Is this the baseline period? | Yes                         |
| Allocation method            | Not applicable              |
| Blinding used                | Not blinded                 |

### Arms

|           |            |
|-----------|------------|
| Arm title | ivabradine |
|-----------|------------|

Arm description:

ivabradine 7.5 mg

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | test drug         |
| Investigational medicinal product name | ivabradine 7.5 mg |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

1 tablet twice daily during meals

|                                       |            |
|---------------------------------------|------------|
| <b>Number of subjects in period 1</b> | ivabradine |
| Started                               | 15         |
| Completed                             | 15         |



## Baseline characteristics

### Reporting groups

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

Reporting group description: -

| Reporting group values | Ivabradine | Total |  |
|------------------------|------------|-------|--|
| Number of subjects     | 15         | 15    |  |
| Age categorical        |            |       |  |
| Units: Subjects        |            |       |  |
| Adults (18-64 years)   | 5          | 5     |  |
| From 65-84 years       | 10         | 10    |  |
| Age continuous         |            |       |  |
| Units: years           |            |       |  |
| arithmetic mean        | 65.8       |       |  |
| standard deviation     | ± 7.4      | -     |  |
| Gender categorical     |            |       |  |
| Units: Subjects        |            |       |  |
| Female                 | 0          | 0     |  |
| Male                   | 15         | 15    |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                          |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                    | ivabradine         |
| Reporting group description:<br>ivabradine 7.5 mg                                                                                                                                                                                                                                                                        |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                               | Included Set       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                | Intention-to-treat |
| Subject analysis set description:<br>All included patients                                                                                                                                                                                                                                                               |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                               | Full Analysis Set  |
| Subject analysis set type                                                                                                                                                                                                                                                                                                | Full analysis      |
| Subject analysis set description:<br>All included patients having received at least one study drug intake and having a strain value at baseline and at W2 visit, at each time point (at rest, at peak and at 3 minutes of recovery) for at least one segment showing exercise-inducible myocardial stunning at baseline. |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                               | Safety Set         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                | Safety analysis    |
| Subject analysis set description:<br>All included patients having received at least one study drug intake.                                                                                                                                                                                                               |                    |

### Primary: Post-ischaemic myocardial stunning

|                                                                                                                                                                                                                                                                                                                      |                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                      | Post-ischaemic myocardial stunning <sup>[1]</sup> |
| End point description:<br>By using bi-dimensional echocardiography at rest and at peak of exercise and during the recovery phase, a strain value (%) was measured for 16 segments of the LV myocardial wall. The segments showing post-ischaemic myocardial stunning at baseline were assessed for efficacy results. |                                                   |
| End point type                                                                                                                                                                                                                                                                                                       | Primary                                           |
| End point timeframe:<br>The primary endpoint was the post-ischaemic myocardial stunning evaluating changes (%) in regional myocardial wall motion from rest to peak exercise and to recovery time points (3 min, 10 min, 20 min). Change from baseline to W2 was provided.                                           |                                                   |

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: only descriptive analyses were done

| End point values                                                             | Full Analysis Set    |  |  |  |
|------------------------------------------------------------------------------|----------------------|--|--|--|
| Subject group type                                                           | Subject analysis set |  |  |  |
| Number of subjects analysed                                                  | 15                   |  |  |  |
| Units: strain relative change from rest arithmetic mean (standard deviation) |                      |  |  |  |
| change from baseline at peak                                                 | 23.1 (± 16.3)        |  |  |  |
| change from baseline at 3 min recovery                                       | 20.1 (± 12.3)        |  |  |  |
| change from baseline at 10 min recovery                                      | 10.3 (± 13.9)        |  |  |  |
| change from baseline at 20 min recovery                                      | 2.2 (± 10.6)         |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

All over the study

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | ivabradine |
|-----------------------|------------|

Reporting group description: -

| Serious adverse events                            | ivabradine     |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 15 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | ivabradine     |  |  |
|-------------------------------------------------------|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 0 / 15 (0.00%) |  |  |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Low number of patients receiving the study drug and short duration of the treatment period.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 October 2012 | To extend the enrolment period by one year from October 2012 to October 2013.<br>-To update information on concomitant treatments and the list of adverse events for which specific information was requested and already collected, if any. |
| 11 July 2013    | -To extent the enrolment period by ten months from October 2013 to August 2014<br>To clarify a study procedure regarding the blood sampling results to be checked by the investigator before the inclusion of the patient                    |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported