



## Clinical trial results:

### Effect of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with Preserved left ventricular Ejection Fraction

An 8-month, randomised double-blind, placebo controlled, international, multicentre study.

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2012-002742-20                   |
| Trial protocol           | HU PT IT DE BE GB NL ES CZ AT SI |
| Global end of trial date | 29 February 2016                 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 04 March 2017 |
| First version publication date | 04 March 2017 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL2-16257-101 |
|-----------------------|---------------|

##### 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               | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com |
| Scientific contact           | Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com |
| Sponsor organisation name    | Laboratorios Servier SL   |
| Sponsor organisation address | Avd de los Madronos 33, Madrid, Spain, 28043  |
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| Sponsor organisation name    | Servier Research and Development Ltd  |
| Sponsor organisation address | Rowley, Wexham Springs, Framewood Road, Wexham, United Kingdom, Slough SL3 6PJ  |
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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                       | 29 February 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 29 February 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 February 2016 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

### General information about the trial

Main objective of the trial:

To assess the effect of ivabradine compared to placebo on the cardiac function, the exercise capacity and the neuroendocrine activation in patients with chronic heart failure over an 8-month treatment period.

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.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 25 June 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 | Argentina: 6       |
| Country: Number of subjects enrolled | Australia: 5       |
| Country: Number of subjects enrolled | Belgium: 2         |
| Country: Number of subjects enrolled | Brazil: 5          |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | France: 3          |
| Country: Number of subjects enrolled | Germany: 18        |

|                                      |   |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Hungary: 20                               |
| Country: Number of subjects enrolled | Ireland: 1                                |
| Country: Number of subjects enrolled | Italy: 5                                  |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 7 |
| Country: Number of subjects enrolled | Netherlands: 6                            |
| Country: Number of subjects enrolled | Poland: 13                                |
| Country: Number of subjects enrolled | Portugal: 3                               |
| Country: Number of subjects enrolled | Russian Federation: 32                    |
| Country: Number of subjects enrolled | Slovenia: 2                               |
| Country: Number of subjects enrolled | Spain: 19                                 |
| Country: Number of subjects enrolled | Taiwan: 8                                 |
| Country: Number of subjects enrolled | United Kingdom: 14                        |
| Worldwide total number of subjects   | 179                                       |
| EEA total number of subjects         | 116                                       |

Notes:

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### 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)                      | 34  |
| From 65 to 84 years                       | 136 |
| 85 years and over                         | 9   |

## Subject disposition

### Recruitment

Recruitment details:

The number of patients included was substantially less (45%) than the 400 proposed in the protocol because of the difficulties in meeting the strict selection criteria designed to ensure to select an appropriate HFPEF population.

### Pre-assignment

Screening details:

Patients were men or women aged at least 50 years with Chronic HF and preserved Ejection Fraction (HF-PEF) and HR  $\geq$  70 bpm.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | double-blind treatment period (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        |
| <b>Arm title</b>             | Ivabradine |

Arm description:

Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals.

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

Dosage and administration details:

Ivabradine tablets were administered twice daily (morning and evening) during meals with a starting dose of 5 mg twice daily.

The dose of ivabradine could be titrated depending on the patient's ECG resting HR and tolerability to a lower dose (2.5 mg) or a higher dose (7.5 mg b.i.d. then 10 mg b.i.d. before Amendment No. 8). This could be done at any visit and multiple titrations were permitted.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Matching placebo |
|------------------|------------------|

Arm description:

Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.

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

Matching placebo tablets were administered twice daily (morning and evening) during meals with a starting dose of 5 mg twice daily.

The dose of placebo could be titrated depending on the patient's ECG resting HR and tolerability to a lower dose (2.5 mg) or a higher dose (7.5 mg b.i.d. then 10 mg b.i.d. before Amendment No. 8). This could be done at any visit and multiple titrations were permitted.

| <b>Number of subjects in period 1</b> | Ivabradine | Matching placebo |
|---------------------------------------|------------|------------------|
| Started                               | 95         | 84               |
| Completed                             | 76         | 77               |
| Not completed                         | 19         | 7                |
| Adverse event, serious fatal          | 3          | -                |
| Non medical reason                    | 6          | 2                |
| Adverse event, non-fatal              | 8          | 5                |
| Other reason                          | 1          | -                |
| Protocol deviation                    | 1          | -                |

## Baseline characteristics

### Reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Ivabradine       |
| Reporting group description:  |                  |
| Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals. |                  |
| Reporting group title   | Matching placebo |
| Reporting group description:  |                  |
| Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.                  |                  |

| Reporting group values | Ivabradine | Matching placebo | Total |
|------------------------|------------|------------------|-------|
| Number of subjects     | 95         | 84               | 179   |
| Age categorical        |            |                  |       |
| Units: Subjects        |            |                  |       |
| Adults (18-64 years)   | 18         | 16               | 34    |
| From 65-84 years       | 70         | 66               | 136   |
| 85 years and over      | 7          | 2                | 9     |
| Age continuous         |            |                  |       |
| Units: years           |            |                  |       |
| arithmetic mean        | 71.4       | 71.8             |       |
| standard deviation     | ± 8.6      | ± 9.3            | -     |
| Gender categorical     |            |                  |       |
| Units: Subjects        |            |                  |       |
| Female                 | 59         | 57               | 116   |
| Male                   | 36         | 27               | 63    |

### Subject analysis sets

|   |                    |
|---|--------------------|
| Subject analysis set title                                    | Randomized Set     |
| Subject analysis set type                                     | Intention-to-treat |
| Subject analysis set description:                             |                    |
| All patients to whom a therapeutic unit was randomly assigned |                    |

| Reporting group values | Randomized Set |  |  |
|------------------------|----------------|--|--|
| Number of subjects     | 179            |  |  |
| Age categorical        |                |  |  |
| Units: Subjects        |                |  |  |
| Adults (18-64 years)   | 34             |  |  |
| From 65-84 years       | 136            |  |  |
| 85 years and over      | 9              |  |  |
| Age continuous         |                |  |  |
| Units: years           |                |  |  |
| arithmetic mean        | 71.6           |  |  |
| standard deviation     | ± 8.9          |  |  |
| Gender categorical     |                |  |  |
| Units: Subjects        |                |  |  |
| Female                 | 116            |  |  |
| Male                   | 63             |  |  |



## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Ivabradine         |
| Reporting group description:  |                    |
| Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals. |                    |
| Reporting group title   | Matching placebo   |
| Reporting group description:  |                    |
| Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.                  |                    |
| Subject analysis set title  | Randomized Set     |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:   |                    |
| All patients to whom a therapeutic unit was randomly assigned   |                    |

### Primary: E/e' – Change from baseline to last post-baseline

|   |   |
|---|---|
| End point title   | E/e' – Change from baseline to last post-baseline |
| End point description:  |   |
| Co-primary endpoint: (E= early diastolic mitral flow velocity, e'= mean of mitral annular lateral and septal proto diastolic velocities) an estimate of LV filling pressures based on Echo-Doppler measures.                          |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| A comprehensive transthoracic echocardiography was performed at the ASSE, M2 and M8 visits. The E/e' ratio was described in terms of value at baseline, last post-baseline value and change from baseline to last post-baseline value |   |

| End point values                     | Ivabradine      | Matching placebo |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 84              | 83               |  |  |
| Units: no unit                       |                 |                  |  |  |
| arithmetic mean (standard deviation) | 0.9 (± 3.8)     | -0.9 (± 6.4)     |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Ivabradine versus placebo effect         |
| Comparison groups                       | Ivabradine v Matching placebo            |
| Number of subjects included in analysis | 167                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.135 <sup>[1]</sup>                   |
| Method                                  | Ancova adj. on geogra. area and baseline |
| Parameter estimate                      | Arithmetic group means (final values)    |
| Point estimate                          | 1.37                                     |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 90 %                       |
| sides                | 2-sided                    |
| lower limit          | 0.25                       |
| upper limit          | 2.49                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.68                       |

Notes:

[1] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

### Primary: Total distance in 6MWT – Change from baseline to last post-baseline

|   |   |
|---|---|
| End point title   | Total distance in 6MWT – Change from baseline to last post-baseline |
| End point description:  |   |
| Co-primary endpoint.  |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| The total distance walked in 6 minutes was performed at ASSE, D000, M002, M004 and M008. The 6MWT was described in terms of value at baseline, last post baseline value and change from baseline to last post-baseline value. |   |

| End point values                     | Ivabradine      | Matching placebo |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 84              | 84               |  |  |
| Units: meter                         |                 |                  |  |  |
| arithmetic mean (standard deviation) | 4.3 (± 50)      | 7.9 (± 67.9)     |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Ivabradine versus placebo effect         |
| Comparison groups                       | Ivabradine v Matching placebo            |
| Number of subjects included in analysis | 168                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.882 <sup>[2]</sup>                   |
| Method                                  | Ancova adj. on geogra. area and baseline |
| Parameter estimate                      | Arithmetic group means (final values)    |
| Point estimate                          | -3.75                                    |
| Confidence interval                     |  |
| level                                   | 90 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -19.14                                   |
| upper limit                             | 11.64                                    |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 9.3                                      |

Notes:

[2] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

### Primary: NT-proBNP – Change from baseline to last post-baseline

|                 |  |
|-----------------|--|
| End point title | NT-proBNP – Change from baseline to last post-baseline |
|-----------------|--|

End point description:

Co-primary endpoint: Plasma concentration of N Terminal-pro Beta type Natriuretic Peptide centrally measured using blood samples.

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

End point timeframe:

NT-proBNP samples collected at D000 (baseline value), M002, M004 and M008. Log-transformation of mean values at baseline and last post-baseline value; change calculated as ratio of baseline value to post-baseline value.

| End point values                              | Ivabradine       | Matching placebo |  |  |
|---|------------------|------------------|--|--|
| Subject group type                            | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                   | 83               | 82               |  |  |
| Units: pg/mL                                  |                  |                  |  |  |
| geometric mean (inter-quartile range (Q1-Q3)) | 1.1 (0.8 to 1.5) | 1.1 (0.8 to 1.4) |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Ivabradine versus placebo effect         |
| Comparison groups                       | Ivabradine v Matching placebo            |
| Number of subjects included in analysis | 165                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.882 <sup>[3]</sup>                   |
| Method                                  | Ancova adj. on geogra. area and baseline |
| Parameter estimate                      | Geometric group means (final values)     |
| Point estimate                          | 1.01                                     |
| Confidence interval                     |  |
| level                                   | 90 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.86                                     |
| upper limit                             | 1.19                                     |

Notes:

[3] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment were defined as all adverse events that occurred or worsened (in terms of intensity) or became serious between the first IMP intake date and the last IMP intake date +2 days (both included)

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### 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   | 21 / 84 (25.00%) | 33 / 94 (35.11%) |  |
| number of deaths (all causes)                                       | 0                | 3                |  |
| number of deaths resulting from adverse events                      | 0                | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Basal cell carcinoma  |                  |                  |  |
| subjects affected / exposed   | 1 / 84 (1.19%)   | 1 / 94 (1.06%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Chronic myeloid leukaemia   |                  |                  |  |
| subjects affected / exposed   | 0 / 84 (0.00%)   | 1 / 94 (1.06%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma                                       |                  |                  |  |
| subjects affected / exposed   | 0 / 84 (0.00%)   | 1 / 94 (1.06%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 1            |  |
| Invasive ductal breast carcinoma                                    |                  |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular disorders                              |                |                |  |
| Aortic thrombosis                               |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Deep vein thrombosis                            |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypertension                                    |                |                |  |
| subjects affected / exposed                     | 2 / 84 (2.38%) | 3 / 94 (3.19%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypertensive crisis                             |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Peripheral arterial occlusive disease           |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders        |                |                |  |
| Postmenopausal haemorrhage                      |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Acute pulmonary oedema                          |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Asthma  |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 2 / 94 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| Blood pressure increased                        |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Electrocardiogram QT prolonged                  |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (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  |                |                |  |
| Anaemia postoperative                           |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Fall  |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Muscle rupture                                  |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Angina unstable                                 |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 2 / 94 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 5 / 84 (5.95%) | 5 / 94 (5.32%) |  |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 6          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bradycardia                                     |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bundle branch block left                        |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure                                 |                |                |  |
| subjects affected / exposed                     | 5 / 84 (5.95%) | 6 / 94 (6.38%) |  |
| occurrences causally related to treatment / all | 0 / 5          | 1 / 8          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure acute                           |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure chronic                         |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 84 (1.19%) | 2 / 94 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Mitral valve incompetence                       |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Myocardial infarction                           |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 2 / 94 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tricuspid valve incompetence                    |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ventricular tachycardia                         |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (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                        |                |                |  |
| Dizziness                                       |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypoaesthesia                                   |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| 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 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Syncope   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Transient ischaemic attack                      |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular encephalopathy                         |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| 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            |                |                |  |
| Iron deficiency anaemia                         |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ear and labyrinth disorders                     |                |                |  |
| Vestibular disorder                             |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye disorders                                   |                |                |  |
| Macular degeneration                            |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Barrett's oesophagus                            |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |



|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diverticulum intestinal haemorrhagic            |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrooesophageal reflux disease                |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| 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                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea  |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oesophageal stenosis                            |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Upper gastrointestinal haemorrhage              |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Chronic kidney disease                          |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal failure                                   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal impairment                                |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| 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 |                |                |  |
| Haemarthrosis                                   |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 0 / 94 (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                     | 2 / 84 (2.38%) | 2 / 94 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal osteoarthritis                           |                |                |  |
| subjects affected / exposed                     | 1 / 84 (1.19%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Lymph node tuberculosis                         |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Mastitis  |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|  |                |                |  |
|--|----------------|----------------|--|
| Respiratory tract infection<br>subjects affected / exposed | 1 / 84 (1.19%) | 0 / 94 (0.00%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all              | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders                         |                |                |  |
| Hyperkalaemia  |                |                |  |
| subjects affected / exposed                                | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0          | 0 / 1          |  |
| deaths causally related to<br>treatment / all              | 0 / 0          | 0 / 0          |  |
| Hyponatraemia  |                |                |  |
| subjects affected / exposed                                | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0          | 0 / 1          |  |
| deaths causally related to<br>treatment / all              | 0 / 0          | 0 / 0          |  |
| Type 2 diabetes mellitus                                   |                |                |  |
| subjects affected / exposed                                | 0 / 84 (0.00%) | 1 / 94 (1.06%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0          | 0 / 1          |  |
| deaths causally related to<br>treatment / all              | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                                      | Placebo          | Ivabradine       |  |
|--|------------------|------------------|--|
| Total subjects affected by non-serious<br>adverse events               |                  |                  |  |
| subjects affected / exposed  | 51 / 84 (60.71%) | 57 / 94 (60.64%) |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                  |                  |  |
| Colon adenoma  |                  |                  |  |
| subjects affected / exposed  | 0 / 84 (0.00%)   | 2 / 94 (2.13%)   |  |
| occurrences (all)  | 0                | 2                |  |
| Vascular disorders   |                  |                  |  |
| Hypertension   |                  |                  |  |
| subjects affected / exposed  | 7 / 84 (8.33%)   | 11 / 94 (11.70%) |  |
| occurrences (all)  | 7                | 11               |  |
| Hypotension  |                  |                  |  |
| subjects affected / exposed  | 1 / 84 (1.19%)   | 2 / 94 (2.13%)   |  |
| occurrences (all)  | 1                | 2                |  |
| General disorders and administration<br>site conditions                |                  |                  |  |

|  |  |  |  |
|--|--|--|--|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 2 / 84 (2.38%)<br>2  | 1 / 94 (1.06%)<br>1  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 84 (0.00%)<br>0  | 4 / 94 (4.26%)<br>4  |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 84 (1.19%)<br>1  | 3 / 94 (3.19%)<br>4  |  |
| Investigations<br>Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Heart rate decreased<br>subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2<br><br>1 / 84 (1.19%)<br>1   | 1 / 94 (1.06%)<br>1<br><br>5 / 94 (5.32%)<br>5   |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2  | 2 / 94 (2.13%)<br>2  |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)<br><br>Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all)<br><br>Bradycardia<br>subjects affected / exposed<br>occurrences (all)<br><br>Cardiac failure<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinus tachycardia | 3 / 84 (3.57%)<br>4<br><br>1 / 84 (1.19%)<br>1<br><br>2 / 84 (2.38%)<br>2<br><br>5 / 84 (5.95%)<br>5 | 2 / 94 (2.13%)<br>2<br><br>2 / 94 (2.13%)<br>2<br><br>3 / 94 (3.19%)<br>3<br><br>2 / 94 (2.13%)<br>2 |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2 | 0 / 94 (0.00%)<br>0 |  |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 84 (0.00%)<br>0 | 2 / 94 (2.13%)<br>2 |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)              | 6 / 84 (7.14%)<br>7 | 2 / 94 (2.13%)<br>2 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2 | 0 / 94 (0.00%)<br>0 |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 84 (0.00%)<br>0 | 2 / 94 (2.13%)<br>2 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 84 (1.19%)<br>1 | 4 / 94 (4.26%)<br>4 |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)             | 2 / 84 (2.38%)<br>2 | 0 / 94 (0.00%)<br>0 |  |
| Eye disorders<br>Photopsia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 84 (0.00%)<br>0 | 3 / 94 (3.19%)<br>3 |  |
| Gastrointestinal disorders<br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 1 / 84 (1.19%)<br>1 | 2 / 94 (2.13%)<br>2 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 84 (2.38%)<br>2 | 1 / 94 (1.06%)<br>1 |  |
| Dental caries<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 84 (0.00%)<br>0 | 2 / 94 (2.13%)<br>2 |  |

|  |  |  |  |
|--|--|--|--|
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 84 (0.00%)<br>0  | 2 / 94 (2.13%)<br>2  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2  | 0 / 94 (0.00%)<br>0  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 2 / 84 (2.38%)<br>2  | 0 / 94 (0.00%)<br>0  |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)  | 2 / 84 (2.38%)<br>2  | 1 / 94 (1.06%)<br>1  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 1 / 84 (1.19%)<br>1<br><br>4 / 84 (4.76%)<br>4   | 2 / 94 (2.13%)<br>2<br><br>0 / 94 (0.00%)<br>0   |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 84 (2.38%)<br>2<br><br>0 / 84 (0.00%)<br>0<br><br>3 / 84 (3.57%)<br>3<br><br>2 / 84 (2.38%)<br>2 | 0 / 94 (0.00%)<br>0<br><br>3 / 94 (3.19%)<br>3<br><br>0 / 94 (0.00%)<br>0<br><br>1 / 94 (1.06%)<br>1 |  |
| Metabolism and nutrition disorders<br>Decreased appetite   |  |  |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 94 (2.13%) |  |
| occurrences (all)           | 0              | 2              |  |
| Hyperuricaemia              |                |                |  |
| subjects affected / exposed | 0 / 84 (0.00%) | 2 / 94 (2.13%) |  |
| occurrences (all)           | 0              | 2              |  |
| Hyperkalaemia               |                |                |  |
| subjects affected / exposed | 2 / 84 (2.38%) | 2 / 94 (2.13%) |  |
| occurrences (all)           | 2              | 2              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 07 October 2013 | <p>Amendment No. 6, was applicable in all countries. The main changes were as following:</p> <ul style="list-style-type: none"><li>- Measurement of pulse rate before the 6MWT, immediately at the end of the test, and at 1 and 10 minutes after the test.</li><li>- Addition of the ventricular-arterial coupling defined by the ratio Ea/Ees as secondary efficacy criterion.</li><li>- Fasting conditions for blood sampling were not required.</li><li>- A dose margin of diuretics within 4 weeks prior to selection was accepted.</li><li>- Addition of large mitral calcifications and of aortic or mitral valvular surgery as non-selection criteria.</li><li>- Rehabilitation program was accepted only if it was started at least 3 months prior to selection, and provided that the patients were under maintenance phase of rehabilitation at selection.</li><li>- Clarification on the biomarkers analysis.</li><li>- Addition of Slovenia as participating country.</li><li>- Planification of the cardiac MRI sub-study in UK.</li><li>- Slight modification of the cut-off of the NT-proBNP and BNP levels as inclusion criteria (NT-proBNP &gt; 300 pg/mL or BNP &gt; 100 pg/mL replaced by <math>\geq 300</math> pg/mL or <math>\geq 100</math> pg/mL respectively).</li><li>- Addition of a check at inclusion that the patient was still able to perform the 6MWT.</li><li>- Atrio-ventricular block of 3rd degree was considered as a contra-indication of the IMP and was consequently a withdrawal criterion.</li><li>- Clarification of the process of echocardiography's review and of the instructions for echocardiography.</li><li>- BioStorage Technologies were named responsible for the long-term storage of non genomic and genomic analyses.</li></ul> |
| 31 March 2014   | <p>Amendment No. 7 was applicable in all countries. The main changes were as following:</p> <ul style="list-style-type: none"><li>- Extension of the enrolment period.</li><li>- Study completion update.</li><li>- Possibility to perform the blood sampling at selection before any other investigations.</li><li>- Decrease of the cut-off of the NT-proBNP and BNP levels (NT-proBNP <math>\geq 220</math> pg/mL or BNP <math>\geq 80</math> pg/mL) as inclusion criteria.</li><li>- The NT-proBNP or BNP values could be checked at the selection visit if the results were available.</li><li>- Decrease of the cut-off of the LVEF (<math>\geq 45\%</math> and <math>&lt; 50\%</math>) as selection criterion.</li><li>- Previous aortic surgery or intervention allowed if at least 1 year before selection.</li><li>- Previous treatment with ivabradine allowed if stopped since at least 6 months before selection.</li><li>- Possibility for patients to be re-enrolled in the study.</li><li>- Decrease of the cut-off of creatinine clearance (<math>&gt; 15</math> and <math>&lt; 30</math> mL/min/1.73m<sup>2</sup>) at selection and inclusion.</li><li>- Setting-up of a Data Monitoring Committee.</li></ul>   |
| 19 June 2014    | <p>Amendment No. 8, was applicable in all countries. The main changes were as following:</p> <ul style="list-style-type: none"><li>- The highest 10 mg dose was removed from the study.</li><li>- Korea and Taiwan were added as participating countries.</li></ul>   |



|                 |  |
|-----------------|--|
| 14 January 2015 | Amendment No. 10, was applicable in all countries. The main changes were as following:<br><ul style="list-style-type: none"> <li>- Intake of the grapefruit juice should be avoided.</li> <li>- Change of the method of calculation of the TEI index and removal of the IVCT criterion.</li> <li>- The 6MWT could be performed before the echocardiography in exceptional circumstances.</li> <li>- The samples for NT-proBNP and other biomarkers analyses were sent on a regular basis to the central laboratory CDL Pharma</li> </ul> |
| 04 May 2015     | Amendment No. 12, was applicable in all countries. An interim analysis was added.  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date           | Interruption   | Restart date |
|----------------|--|--------------|
| 14 August 2015 | The recruitment period was extended for 8 months by Amendment 7, but further prolongation was abandoned. | -            |

Notes:

## Limitations and caveats

None reported