



## Clinical trial results:

**A multicenter, randomized, double-blind, crossover placebo-controlled Phase II study to assess the effect of serelaxin versus placebo on high sensitivity cardiac troponin I (hs-cTnI) release in patients with chronic heart failure after exercise when used in addition to standard of care**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-002673-38  |
| Trial protocol           | GB DE           |
| Global end of trial date | 11 January 2017 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 27 January 2018 |
| First version publication date | 27 January 2018 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRLX030A2211 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02625922 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Pharma AG   |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                   |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

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                       | 11 January 2017 |
| Is this the analysis of the primary completion data? | No              |

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|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 11 January 2017 |
| Was the trial ended prematurely? | Yes             |

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Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the effect of short-term i.v. administration of serelaxin in CHF patients on the geometric mean of high-sensitivity cardiac troponin I (hs-cTnI) concentrations compared to placebo (both in addition to the standard of care) after an exercise testing session.

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Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

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Background therapy: -

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Evidence for comparator: -

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|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 05 February 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Germany: 8         |
| Country: Number of subjects enrolled | Switzerland: 5     |
| Worldwide total number of subjects   | 26                 |
| EEA total number of subjects         | 21                 |

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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)                      | 4 |

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|                     |    |
|---------------------|----|
| From 65 to 84 years | 21 |
| 85 years and over   | 1  |

## Subject disposition

### Recruitment

Recruitment details:

26 subjects were randomized in 11 study sites from 3 countries (Germany, Switzerland, and the United Kingdom).

### Pre-assignment

Screening details:

Patient selection was to be established by checking through all inclusion/exclusion criteria at screening and randomization.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall 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>             | Serelaxin-Placebo |

Arm description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Serelaxin       |
| Investigational medicinal product code |                 |
| Other name                             | RLX030          |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Serelaxin will be administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Placebo         |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Matching placebo i.v infusion.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo-Serelaxin |
|------------------|-------------------|

Arm description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Placebo         |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Matching placebo i.v infusion.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Serelaxin       |
| Investigational medicinal product code |                 |
| Other name                             | RLX030          |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Serelaxin will be administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

| <b>Number of subjects in period 1</b> | Serelaxin-Placebo | Placebo-Serelaxin |
|---------------------------------------|-------------------|-------------------|
| Started                               | 14                | 12                |
| Completed                             | 12                | 10                |
| Not completed                         | 2                 | 2                 |
| Non-availability of IMP               | 1                 | 1                 |
| Systolic blood pressure < 125 mmHg    | 1                 | 1                 |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

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

Reporting group description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

| Reporting group values                             | Serelaxin-Placebo | Placebo-Serelaxin | Total |
|--|-------------------|-------------------|-------|
| Number of subjects                                 | 14                | 12                | 26    |
| 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)                               | 1                 | 3                 | 4     |
| From 65-84 years                                   | 12                | 9                 | 21    |
| 85 years and over                                  | 1                 | 0                 | 1     |
| Age continuous                                     |                   |                   |       |
| Units: years                                       |                   |                   |       |
| arithmetic mean                                    | 74.7              | 66.5              |       |
| standard deviation                                 | ± 7.62            | ± 13.89           | -     |
| Gender categorical                                 |                   |                   |       |
| Units: Subjects                                    |                   |                   |       |
| Female   | 1                 | 2                 | 3     |
| Male   | 13                | 10                | 23    |

## End points

### End points reporting groups

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

Reporting group description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

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

Reporting group description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

|                            |           |
|----------------------------|-----------|
| Subject analysis set title | Serelaxin |
|----------------------------|-----------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Participants receiving serelaxin in Treatment Period 1 and in Treatment Period 2. Each participant received each of the treatments in randomized order in 2 treatment periods separated by a 15 +/- 1-day washout. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

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

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Participants receiving placebo in Treatment Period 1 and in Treatment Period 2. Each participant received each of the treatments in randomized order in 2 treatment periods separated by a 15 +/- 1-day washout. Placebo was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

### Primary: Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentration After Exercise Compared to Placebo

|                 |   |
|-----------------|---|
| End point title | Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentration After Exercise Compared to Placebo <sup>[1]</sup> |
|-----------------|---|

End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

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

End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15+/- 1)

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: The primary analysis of mixed model repeated measures was not performed because the validation of the primary endpoint variable hs-cTnI assay (Singulex Erenna®) was not completed because of the early termination of the study and, therefore, hs-cTnI was not analyzed.

| End point values                               | Serelaxin-<br>Placebo | Placebo-<br>Serelaxin |  |  |
|--|-----------------------|-----------------------|--|--|
| Subject group type                             | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed                    | 0 <sup>[2]</sup>      | 0 <sup>[3]</sup>      |  |  |
| Units: Overall Number of Participants Analyzed |                       |                       |  |  |

Notes:

[2] - Primary endpoint variable hs-cTnI assay was not completed due to the early termination of the study.

[3] - Primary endpoint variable hs-cTnI assay was not completed due to the early termination of the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentrations After Exercise Compared to Placebo at 4 and 5 Hours

|                 |  |
|-----------------|--|
| End point title | Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentrations After Exercise Compared to Placebo at 4 and 5 Hours |
|-----------------|--|

End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

4 and 5 hours after exercise testing session

| End point values                               | Serelaxin-<br>Placebo | Placebo-<br>Serelaxin |  |  |
|--|-----------------------|-----------------------|--|--|
| Subject group type                             | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed                    | 0 <sup>[4]</sup>      | 0 <sup>[5]</sup>      |  |  |
| Units: Overall Number of Participants Analyzed |                       |                       |  |  |

Notes:

[4] - Endpoint variable hs-cTnI assay was not analyzed due to the early termination of the study.

[5] - Endpoint variable hs-cTnI assay was not analyzed due to the early termination of the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Log-transformed Concentration of N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP) Concentrations Compared to Placebo

|                 |   |
|-----------------|---|
| End point title | Log-transformed Concentration of N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP) Concentrations Compared to Placebo |
|-----------------|---|

End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15 +/- 1)



| End point values                     | Serelaxin            | Placebo              |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 26 <sup>[6]</sup>    | 26 <sup>[7]</sup>    |  |  |
| Units: pg/mL                         |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline                             | 13.5026 (± 0.64893)  | 13.6217 (± 0.60192)  |  |  |
| 132 minutes                          | 13.5729 (± 0.62057)  | 13.7076 (± 0.61612)  |  |  |
| 180 minutes                          | 15.5302 (± 0.62107)  | 13.6777 (± 0.61118)  |  |  |
| 240 minutes                          | 13.5673 (± 0.68419)  | 13.7011 (± 0.58471)  |  |  |
| 300 minutes                          | 13.6103 (± 0.63614)  | 13.7129 (± 0.57832)  |  |  |
| 360 minutes                          | 13.6687 (± 0.65735)  | 13.7213 (± 0.57366)  |  |  |
| 420 minutes                          | 16.6533 (± 0.64776)  | 13.7399 (± 0.57361)  |  |  |

Notes:

[6] - The full analysis set (FAS) consisted of all randomized patients.

[7] - The full analysis set (FAS) consisted of all randomized patients.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Log-transformed Concentration Values of Heart-type Fatty Acid-binding Protein (H-FABP) Concentrations Compared to Placebo

|                 |   |
|-----------------|---|
| End point title | Log-transformed Concentration Values of Heart-type Fatty Acid-binding Protein (H-FABP) Concentrations Compared to Placebo |
|-----------------|---|

End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15 +/- 1).

| End point values                     | Serelaxin            | Placebo              |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 26 <sup>[8]</sup>    | 26 <sup>[9]</sup>    |  |  |
| Units: ng/mL                         |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline                             | 8.8256 (± 0.67027)   | 8.8810 (± 0.64372)   |  |  |
| 132 minutes                          | 8.8644 (± 0.63646)   | 8.8409 (± 0.67261)   |  |  |

|             |                            |                            |  |  |
|-------------|----------------------------|----------------------------|--|--|
| 180 minutes | 8.7897 ( $\pm$<br>0.62835) | 8.7955 ( $\pm$<br>0.62729) |  |  |
| 240 minutes | 8.7718 ( $\pm$<br>0.63971) | 8.8662 ( $\pm$<br>0.58565) |  |  |
| 300 minutes | 8.7309 ( $\pm$<br>0.62177) | 8.7202 ( $\pm$<br>0.65890) |  |  |
| 360 minutes | 8.7692 ( $\pm$<br>0.64920) | 8.8088 ( $\pm$<br>0.59672) |  |  |
| 420 minutes | 8.7669 ( $\pm$<br>0.65793) | 8.7329 ( $\pm$<br>0.63139) |  |  |

Notes:

[8] - The full analysis set (FAS) consisted of all randomized patients.

[9] - The full analysis set (FAS) consisted of all randomized patients.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are monitored from on or after the time of first administration of study treatment up to 30 days after the last administration were included.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.0   |

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Serelaxin |
|-----------------------|-----------|

Reporting group description:

Serelaxin

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

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

Reporting group description:

Placebo

| Serious adverse events                            | Serelaxin      | Total          | Placebo        |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 20 (0.00%) | 1 / 22 (4.55%) | 1 / 20 (5.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    | 0              | 0              | 0              |
| Musculoskeletal and connective tissue disorders   |                |                |                |
| Haemarthrosis                                     |                |                |                |
| subjects affected / exposed                       | 0 / 20 (0.00%) | 1 / 22 (4.55%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events                            | Serelaxin       | Total            | Placebo         |
|---|-----------------|------------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                  |                 |
| subjects affected / exposed                           | 7 / 20 (35.00%) | 12 / 22 (54.55%) | 6 / 20 (30.00%) |
| Vascular disorders                                    |                 |                  |                 |

|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| Hypotension<br>subjects affected / exposed<br>occurrences (all)  | 2 / 20 (10.00%)<br>2 | 2 / 22 (9.09%)<br>2 | 0 / 20 (0.00%)<br>0 |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 20 (5.00%)<br>1  | 1 / 22 (4.55%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1 | 1 / 20 (5.00%)<br>1 |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 1 / 22 (4.55%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 20 (5.00%)<br>1  | 1 / 22 (4.55%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Inguinal hernia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1 | 1 / 20 (5.00%)<br>1 |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>1  | 1 / 22 (4.55%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 20 (5.00%)<br>1  | 1 / 22 (4.55%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1 | 1 / 20 (5.00%)<br>1 |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 20 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1 | 1 / 20 (5.00%)<br>1 |
| Renal and urinary disorders  |                      |                     |                     |

|   |   |   |   |
|---|---|---|---|
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0   | 1 / 22 (4.55%)<br>1   | 1 / 20 (5.00%)<br>1   |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1   | 1 / 22 (4.55%)<br>1   | 0 / 20 (0.00%)<br>0   |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>1 / 20 (5.00%)<br>1 | 1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1<br><br>1 / 22 (4.55%)<br>1 | 1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>0 / 20 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Iron deficiency<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1   | 1 / 22 (4.55%)<br>1   | 0 / 20 (0.00%)<br>0   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 27 October 2015  | <ul style="list-style-type: none"><li>Updated the assessment of pregnancy according to new information from preclinical studies and the updated Investigator's Brochure. An additional time point for the pregnancy test was included</li><li>Updated the list of exclusion criteria. Exclusion criterion 2 was removed because the patient population was defined as stable based on inclusion criterion 3 and exclusion criterion 6</li><li>Clarified that the Data Monitoring Committee could not terminate the study independently, but could only issue a recommendation to the Sponsor</li><li>Provided clarification on the reporting of AEs during the study</li><li>Improved the clarity of the description and graphic representation of the Borg CR10 scale and the echocardiography</li></ul>  |
| 20 December 2016 | <ul style="list-style-type: none"><li>Adjusted inclusion criterion 4 and defined left ventricular ejection fraction &lt; 50% according to the updated heart failure guidelines of the European Society of Cardiology</li><li>Adjusted inclusion criterion 5 to NT-proBNP &gt; 250 ng/L</li><li>Adjusted exclusion criterion 14 to exclude patients with a history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy less than 1 year</li><li>Removed exclusion criterion 4 and accounted for the fact that the primary purpose of the Screening exercise test was to calculate a workload that would stress the patient but allowed them to complete the 12-minute exercise at Treatment Periods 1 and 2. Therefore, maximum capacity threshold of VCO<sub>2</sub>/VO<sub>2</sub> &gt; 1.05 was not to be an exclusion criterion per se</li><li>Updated exclusion criterion 17 to match the description of highly effective contraception methods in the current template</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The study was terminated early by Novartis, 19-Apr-2017. Because of the early termination of the study, the validation of the hs-cTnI assay was not completed and the primary efficacy endpoint was not analyzed.

Notes: