



## Clinical trial results:

**A multicenter, prospective, randomized, open label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients**

### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2013-002513-35  |
| Trial protocol           | GB AT HU IT CZ SK BE PT BG LT PL LV EE FI SI GR ES HR DK IS |
| Global end of trial date | 5 April 2017  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 10 May 2018  |
| First version publication date | 10 May 2018  |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRLX030A3301 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02064868 |
| 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, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 25 April 2017 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 25 April 2017 |
| Was the trial ended prematurely? | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of serelaxin as add-on therapy to standard of care (SOC) versus SOC alone in reducing in-hospital worsening heart failure (WHF) requiring rescue therapy or all-cause death, from randomization through Day 5.

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.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 31 January 2014 |
| 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 | Austria: 56             |
| Country: Number of subjects enrolled | Belgium: 87             |
| Country: Number of subjects enrolled | Bulgaria: 74            |
| Country: Number of subjects enrolled | Croatia: 11             |
| Country: Number of subjects enrolled | Czech Republic: 78      |
| Country: Number of subjects enrolled | Estonia: 26             |
| Country: Number of subjects enrolled | Finland: 1              |
| Country: Number of subjects enrolled | France: 239             |
| Country: Number of subjects enrolled | Germany: 383            |
| Country: Number of subjects enrolled | Greece: 49              |
| Country: Number of subjects enrolled | Hungary: 149            |
| Country: Number of subjects enrolled | Iceland: 8              |
| Country: Number of subjects enrolled | Italy: 225              |
| Country: Number of subjects enrolled | Latvia: 20              |
| Country: Number of subjects enrolled | Lithuania: 40           |
| Country: Number of subjects enrolled | Poland: 166             |
| Country: Number of subjects enrolled | Portugal: 50            |
| Country: Number of subjects enrolled | Romania: 95             |
| Country: Number of subjects enrolled | Russian Federation: 382 |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Serbia: 176        |
| Country: Number of subjects enrolled | Slovakia: 36       |
| Country: Number of subjects enrolled | Slovenia: 17       |
| Country: Number of subjects enrolled | Spain: 207         |
| Country: Number of subjects enrolled | Switzerland: 34    |
| Country: Number of subjects enrolled | United Kingdom: 41 |
| Worldwide total number of subjects   | 2650               |
| EEA total number of subjects         | 2058               |

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)                      | 402  |
| From 65 to 84 years                       | 1751 |
| 85 years and over                         | 497  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The initial target was to randomize 3183 patients. This study was prematurely terminated (due to the neutral read-out of study RELAX-AHF-2) after 2666 patients were randomized. 16 patients had not qualified for randomization but were inadvertently randomized. These 16 patients did not enter the treatment phase and were not counted as started.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Serelaxin + Standard of Care |
|------------------|------------------------------|

Arm description:

Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.

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

Dosage and administration details:

Study drug was administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day, as a continuous intravenous infusion for 48 hours.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Standard of Care (SOC) |
|------------------|------------------------|

Arm description:

All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc.

|   |                  |
|---|------------------|
| Arm type  | Standard of Care |
| No investigational medicinal product assigned in this arm |                  |

| Number of subjects in period 1 | Serelaxin + Standard of Care | Standard of Care (SOC) |
|--------------------------------|------------------------------|------------------------|
| Started                        | 1756                         | 894                    |
| Full Analysis Set              | 1756                         | 894                    |
| Safety Set                     | 1729                         | 894                    |
| Completed                      | 1722                         | 881                    |
| Not completed                  | 34                           | 13                     |
| Physician decision             | 1                            | -                      |

|                               |    |   |
|-------------------------------|----|---|
| Consent withdrawn by subject  | 14 | 3 |
| Technical Problems or Missing | 5  | 2 |
| Lost to follow-up             | 14 | 8 |

## Baseline characteristics

### Reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Serelaxin + Standard of Care |
| Reporting group description:   |                              |
| Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.   |                              |
| Reporting group title  | Standard of Care (SOC)       |
| Reporting group description:   |                              |
| All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc. |                              |

| Reporting group values                             | Serelaxin + Standard of Care | Standard of Care (SOC) | Total |
|--|------------------------------|------------------------|-------|
| Number of subjects                                 | 1756                         | 894                    | 2650  |
| 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)                               | 281                          | 121                    | 402   |
| From 65-84 years                                   | 1151                         | 600                    | 1751  |
| 85 years and over                                  | 324                          | 173                    | 497   |
| Age Continuous                                     |                              |                        |       |
| Units: Years                                       |                              |                        |       |
| arithmetic mean                                    | 75.24                        | 75.95                  |       |
| standard deviation                                 | ± 10.349                     | ± 9.905                | -     |
| Sex: Female, Male                                  |                              |                        |       |
| Units: Subjects                                    |                              |                        |       |
| Female   | 760                          | 383                    | 1143  |
| Male   | 996                          | 511                    | 1507  |
| Race/Ethnicity, Customized                         |                              |                        |       |
| Units: Subjects                                    |                              |                        |       |
| Caucasian  | 1706                         | 869                    | 2575  |
| Black  | 4                            | 4                      | 8     |
| Asian  | 5                            | 2                      | 7     |
| Unknown  | 16                           | 7                      | 23    |
| Other  | 25                           | 12                     | 37    |

## End points

### End points reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Serelaxin + Standard of Care |
| Reporting group description:<br>Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.   |                              |
| Reporting group title  | Standard of Care (SOC)       |
| Reporting group description:<br>All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc. |                              |

### Primary: Worsening heart failure (WHF) / all cause of deaths through day 5

|  |   |
|--|---|
| End point title  | Worsening heart failure (WHF) / all cause of deaths through day 5 |
| End point description:<br>In-hospital WHF through Day 5 post-randomization included worsening signs and/or symptoms of heart failure that required an intensification of intravenous therapy for heart failure or mechanical ventilation, renal or circulatory support. A central event adjudication committee was appointed to oversee the WHF primary endpoint adjudication. |   |
| End point type   | Primary   |
| End point timeframe:<br>5 days   |   |

| End point values                  | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|-----------------------------------|------------------------------|------------------------|--|--|
| Subject group type                | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed       | 1756                         | 894                    |  |  |
| Units: Percentage of Participants |                              |                        |  |  |
| number (not applicable)           | 4.95                         | 6.94                   |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | WHF / all cause of deaths                             |
| Comparison groups                       | Standard of Care (SOC) v Serelaxin + Standard of Care |
| Number of subjects included in analysis | 2650  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0172 <sup>[1]</sup>                               |
| Method                                  | Gehan's generalized Wilcoxon test                     |
| Parameter estimate                      | Hazard ratio (HR)                                     |
| Point estimate                          | 0.71  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.51    |
| upper limit         | 0.98    |

Notes:

[1] - One-sided p-value

## Secondary: In-hospital worsening heart failure/all-cause death/readmission for heart failure through day 14

|                 |  |
|-----------------|--|
| End point title | In-hospital worsening heart failure/all-cause death/readmission for heart failure through day 14 |
|-----------------|--|

End point description:

WHF/death/readmission for heart failure through Day 14. WHF/deaths through Day 5 were adjudicated and confirmed by the Clinical Endpoint Committee, WHF/deaths after Day 5 through Day 14 and readmission through Day 14 were as reported by the investigators.

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

End point timeframe:

14 days

| End point values              | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|-------------------------------|------------------------------|------------------------|--|--|
| Subject group type            | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed   | 1756                         | 894                    |  |  |
| Units: Percentage of Patients |                              |                        |  |  |
| number (not applicable)       | 8.49                         | 10.63                  |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | WHF/death/readmission for heart failure               |
| Comparison groups                       | Serelaxin + Standard of Care v Standard of Care (SOC) |
| Number of subjects included in analysis | 2650  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.0634 [2]  |
| Method                                  | Gehan's generalized Wilcoxon test                     |
| Parameter estimate                      | Hazard ratio (HR)                                     |
| Point estimate                          | 0.79  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.61  |
| upper limit                             | 1.02  |

Notes:

[2] - Two-sided p-value



**Secondary: Persistent sign or symptoms of heart failure / non-improvement at any post baseline visit through day 5**

|  |   |
|--|---|
| End point title  | Persistent sign or symptoms of heart failure / non-improvement at any post baseline visit through day 5 |
| End point description:<br>Persistent or non-improvement in any signs or symptoms of HF at any post baseline visit up to Day 5. |   |
| End point type   | Secondary   |
| End point timeframe:<br>5 days   |   |

| End point values                  | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|-----------------------------------|------------------------------|------------------------|--|--|
| Subject group type                | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed       | 1744                         | 894                    |  |  |
| Units: Percentage of Participants |                              |                        |  |  |
| number (confidence interval 95%)  | 86 (84 to 87)                | 91 (89 to 93)          |  |  |

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Persistent or non-improvement in HF                   |
| Comparison groups                       | Serelaxin + Standard of Care v Standard of Care (SOC) |
| Number of subjects included in analysis | 2638  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.0001  |
| Method                                  | Chi-squared   |

**Secondary: Renal deterioration at any post baseline visit through day 14**

|   |   |
|---|---|
| End point title   | Renal deterioration at any post baseline visit through day 14 |
| End point description:<br>Renal deterioration is defined as > or = 0.3 mg/dL increase from screening in serum creatinine. |   |
| End point type  | Secondary   |
| End point timeframe:<br>14 days   |   |

| End point values                  | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|-----------------------------------|------------------------------|------------------------|--|--|
| Subject group type                | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed       | 1740                         | 889                    |  |  |
| Units: Percentage of Participants |                              |                        |  |  |
| number (confidence interval 95%)  | 36 (34 to 38)                | 44 (40 to 47)          |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Renal Deterioration                                   |
| Comparison groups                       | Serelaxin + Standard of Care v Standard of Care (SOC) |
| Number of subjects included in analysis | 2629  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.0002  |
| Method                                  | Chi-squared   |

### Secondary: Length of index hospital stay

|  |                               |
|--|-------------------------------|
| End point title  | Length of index hospital stay |
| End point description:<br>Length of stay (in hours) is defined as the index hospitalization discharge date and time minus the index hospitalization start date and time. |                               |
| End point type   | Secondary                     |
| End point timeframe:<br>30 Days  |                               |

| End point values                     | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|--------------------------------------|------------------------------|------------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed          | 1756                         | 894                    |  |  |
| Units: hours                         |                              |                        |  |  |
| arithmetic mean (standard deviation) | 251.28 (± 162.368)           | 243.59 (± 160.270)     |  |  |

### Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Length of Index Hospital Stay                         |
| Comparison groups                 | Serelaxin + Standard of Care v Standard of Care (SOC) |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 2650                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.1392                |
| Method                                  | Wilcoxon (Mann-Whitney) |

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**Secondary: Number of patients reported with adverse events as assessment of safety and tolerability of Serelaxin in AHF patients**

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|                 |   |
|-----------------|---|
| End point title | Number of patients reported with adverse events as assessment of safety and tolerability of Serelaxin in AHF patients |
|-----------------|---|

End point description:

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

End point timeframe:

Adverse Events (AE): 5 Days / Serious Adverse Events (SAE): 14 days / All cause deaths 30 days

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| End point values                     | Serelaxin + Standard of Care | Standard of Care (SOC) |  |  |
|--------------------------------------|------------------------------|------------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group        |  |  |
| Number of subjects analysed          | 1729                         | 894                    |  |  |
| Units: Percentage of participants    |                              |                        |  |  |
| number (not applicable)              |                              |                        |  |  |
| Patients with any AE through Day 5   | 58.13                        | 56.04                  |  |  |
| Patients with any SAE through Day 14 | 12.38                        | 11.97                  |  |  |
| All cause deaths through Day 5       | 0.58                         | 0.67                   |  |  |
| All cause deaths through Day 14      | 1.91                         | 2.01                   |  |  |
| All cause deaths through Day 30      | 3.30                         | 4.25                   |  |  |

**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change from baseline in Health-related quality of life, assessed by EuroQoL EQ-5D-5L questionnaire.**

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|                 |   |
|-----------------|---|
| End point title | Change from baseline in Health-related quality of life, assessed by EuroQoL EQ-5D-5L questionnaire. |
|-----------------|---|

End point description:

EQ-5D-5L is a questionnaire designed to assess health status in adults consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The results were converted into a single index value using UK as the reference country for all countries. Range -0.3 (worst possible state) to 1 (best possible state).

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

End point timeframe:

Baseline, Day 5, Day 14

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| <b>End point values</b>              | Serelaxin +<br>Standard of<br>Care | Standard of<br>Care (SOC) |  |  |
|--------------------------------------|------------------------------------|---------------------------|--|--|
| Subject group type                   | Reporting group                    | Reporting group           |  |  |
| Number of subjects analysed          | 1545 <sup>[3]</sup>                | 793 <sup>[4]</sup>        |  |  |
| Units: Points                        |                                    |                           |  |  |
| arithmetic mean (standard deviation) |                                    |                           |  |  |
| Day 5                                | 0.28 (± 0.298)                     | 0.27 (± 0.292)            |  |  |
| Day 14                               | 0.32 (± 0.328)                     | 0.31 (± 0.317)            |  |  |

Notes:

[3] - 1545 Subjects Analyzed at Day 5

1486 Subjects Analyzed at Day 14

[4] - 793 Subjects Analyzed at Day 5

756 Subjects Analyzed at Day 14

### Statistical analyses

| <b>Statistical analysis title</b>       | Change in EQ-5D-5L                                    |
|---|---|
| Statistical analysis description:       |   |
| Day 5                                   |   |
| Comparison groups                       | Serelaxin + Standard of Care v Standard of Care (SOC) |
| Number of subjects included in analysis | 2338  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.3115  |
| Method                                  | Mixed models analysis                                 |

| <b>Statistical analysis title</b>       | Change in EQ-5D-5L                                    |
|---|---|
| Statistical analysis description:       |   |
| Day 14                                  |   |
| Comparison groups                       | Serelaxin + Standard of Care v Standard of Care (SOC) |
| Number of subjects included in analysis | 2338  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.1236  |
| Method                                  | Mixed models analysis                                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs are collected from FPFV until LPLV. All AEs are reported in this record from First Patient First Treatment until LPLV.

For each patient AEs were collected to Day 5 and SAEs to Day 14. Deaths were reported only if an associated (S)AE was recorded.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the SAEs field "number of deaths resulting from adverse events" all those deaths, resulting from SAEs that are deemed to be causally related to treatment.

20 additional deaths in "Serelaxin + SOC" and 18 in "SOC" were recorded outside the reporting period of (S)AEs.

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

### Dictionary used

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

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Serelaxin + SOC |
|-----------------------|-----------------|

Reporting group description:

Serelaxin + SOC

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Standard of Care |
|-----------------------|------------------|

Reporting group description:

Standard of care (SOC)

| Serious adverse events  | Serelaxin + SOC     | Standard of Care   |  |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                     |                    |  |
| subjects affected / exposed   | 214 / 1729 (12.38%) | 107 / 894 (11.97%) |  |
| number of deaths (all causes)                                       | 43                  | 25                 |  |
| number of deaths resulting from adverse events                      | 0                   | 1                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                    |  |
| Bladder transitional cell carcinoma                                 |                     |                    |  |
| subjects affected / exposed   | 0 / 1729 (0.00%)    | 1 / 894 (0.11%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0              |  |
| Colon cancer  |                     |                    |  |
| subjects affected / exposed   | 1 / 1729 (0.06%)    | 0 / 894 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 1               | 0 / 0              |  |
| Gastric cancer  |                     |                    |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Leiomyoma                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lung neoplasm malignant                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Plasma cell myeloma                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Prostate cancer metastatic                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vascular disorders                              |                  |                 |  |
| Aortic stenosis                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arterial disorder                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arterial stenosis                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arteriosclerosis                                |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Arteriovenous fistula                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Circulatory collapse                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Femoral artery aneurysm                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematoma                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypertension                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Hypertensive crisis                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypotension                                     |                  |                 |  |
| subjects affected / exposed                     | 7 / 1729 (0.40%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 3 / 7            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Peripheral artery thrombosis                    |                  |                 |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| subjects affected / exposed                          | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral ischaemia                                 |                  |                 |  |
| subjects affected / exposed                          | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Shock haemorrhagic                                   |                  |                 |  |
| subjects affected / exposed                          | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Surgical and medical procedures                      |                  |                 |  |
| Left atrial appendage occlusion                      |                  |                 |  |
| subjects affected / exposed                          | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| Death  |                  |                 |  |
| subjects affected / exposed                          | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 1           |  |
| Fatigue  |                  |                 |  |
| subjects affected / exposed                          | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 0           |  |
| Hyperthermia   |                  |                 |  |
| subjects affected / exposed                          | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Non-cardiac chest pain                               |                  |                 |  |
| subjects affected / exposed                          | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| Organ failure                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Pyrexia   |                  |                 |  |
| subjects affected / exposed                     | 4 / 1729 (0.23%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sudden cardiac death                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Sudden death                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Systemic inflammatory response syndrome         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Acute pulmonary oedema                          |                  |                 |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute respiratory distress syndrome             |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute respiratory failure                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Chronic obstructive pulmonary disease           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dyspnoea  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 3 / 894 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haemothorax                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypercapnia                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 2 / 894 (0.22%) |  |
| 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 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary hypertension                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary mass                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary oedema                                |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory disorder                            |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory distress                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory failure                             |                  |                 |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0           |  |
| Psychiatric disorders                           |                  |                 |  |
| Agitation                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Confusional state                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Delirium  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Investigations                                  |                  |                 |  |
| Blood bilirubin increased                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood creatinine increased                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Electrocardiogram T wave inversion              |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haemoglobin decreased                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Heart rate decreased                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| International normalised ratio decreased        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| International normalised ratio increased        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Liver function test increased                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oxygen saturation decreased                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Injury, poisoning and procedural complications  |                  |                 |  |
| Abdominal injury                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Ankle fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Craniocerebral injury                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Fall  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Femoral neck fracture                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematuria traumatic                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Head injury                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hip fracture                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lumbar vertebral fracture                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Post procedural haemorrhage                     |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Procedural pneumothorax                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Subdural haemorrhage                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Toxicity to various agents                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Traumatic haematoma                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vascular pseudoaneurysm                         |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac disorders                               |                  |                 |  |
| Acute coronary syndrome                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute left ventricular failure                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute myocardial infarction                     |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 6 / 1729 (0.35%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2           |  |
| Angina pectoris                                 |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Angina unstable                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Aortic valve incompetence                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Aortic valve stenosis                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 3 / 894 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrial fibrillation                             |                  |                 |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrioventricular block complete                 |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| Atrioventricular block second degree            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bradyarrhythmia                                 |                  |                 |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1729 (0.12%)  | 0 / 894 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bradycardia                                     |                   |                  |  |
| subjects affected / exposed                     | 7 / 1729 (0.40%)  | 2 / 894 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bundle branch block left                        |                   |                  |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%)  | 1 / 894 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cardiac arrest                                  |                   |                  |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%)  | 2 / 894 (0.22%)  |  |
| occurrences causally related to treatment / all | 1 / 6             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 2            |  |
| Cardiac failure                                 |                   |                  |  |
| subjects affected / exposed                     | 38 / 1729 (2.20%) | 26 / 894 (2.91%) |  |
| occurrences causally related to treatment / all | 1 / 39            | 0 / 26           |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 8            |  |
| Cardiac failure acute                           |                   |                  |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%)  | 2 / 894 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1            |  |
| Cardiac failure chronic                         |                   |                  |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%)  | 1 / 894 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Cardiac failure congestive                      |                   |                  |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%)  | 1 / 894 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Cardiac hypertrophy                             |                   |                  |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Cardiac ventricular thrombosis                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Cardio-respiratory arrest                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cardiogenic shock                               |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Cardiopulmonary failure                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cardiorenal syndrome                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cardiovascular insufficiency                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Congestive cardiomyopathy                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery disease                         |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 7 / 1729 (0.40%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery stenosis                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diastolic dysfunction                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Left ventricular failure                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Mitral valve incompetence                       |                  |                 |  |
| subjects affected / exposed                     | 5 / 1729 (0.29%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myocardial infarction                           |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 3 / 894 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2           |  |
| Myocardial ischaemia                            |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myocarditis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Right ventricular failure                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Sinus arrest                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Stress cardiomyopathy                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tachycardia                                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ventricular fibrillation                        |                  |                 |  |
| subjects affected / exposed                     | 5 / 1729 (0.29%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1           |  |
| Ventricular tachycardia                         |                  |                 |  |
| subjects affected / exposed                     | 5 / 1729 (0.29%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nervous system disorders                        |                  |                 |  |
| Brain oedema                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Carotid artery stenosis                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cerebrovascular accident                        |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Depressed level of consciousness                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Epilepsy  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypercapnic coma                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| 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                     | 3 / 1729 (0.17%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Loss of consciousness                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Seizure   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Status epilepticus                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Anaemia   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Microcytic anaemia                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Glaucoma  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Abdominal pain lower                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal strangulated hernia                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenal ulcer haemorrhage                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dysphagia                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intestinal ischaemia                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0           |  |
| Melaena   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nausea  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vomiting  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders                         |                  |                 |  |
| Cholecystitis                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholelithiasis                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatitis toxic                                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Dermatitis exfoliative                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal and urinary disorders                     |                  |                 |  |
| Acute kidney injury                             |                  |                 |  |
| subjects affected / exposed                     | 9 / 1729 (0.52%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1           |  |
| Acute prerenal failure                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anuria  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chronic kidney disease                          |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematuria                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nephropathy                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nephropathy toxic                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nephrotic syndrome                              |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Prerenal failure                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal failure                                   |                  |                 |  |
| subjects affected / exposed                     | 6 / 1729 (0.35%) | 3 / 894 (0.34%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Renal impairment                                |                  |                 |  |
| subjects affected / exposed                     | 4 / 1729 (0.23%) | 5 / 894 (0.56%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Renal tubular necrosis                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Urinary retention                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Endocrine disorders                             |                  |                 |  |
| Hypothyroidism                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                  |                 |  |
| Chest wall haematoma                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| Joint swelling                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Muscle haemorrhage                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rhabdomyolysis                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Bacteraemia                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchitis                                      |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Diverticulitis                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Escherichia urinary tract infection             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infection                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lower respiratory tract infection               |                  |                 |  |

|   |                   |                 |  |
|---|-------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Nosocomial infection                            |                   |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Oropharyngitis fungal                           |                   |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Parainfluenzae virus infection                  |                   |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Pneumonia                                       |                   |                 |  |
| subjects affected / exposed                     | 11 / 1729 (0.64%) | 6 / 894 (0.67%) |  |
| occurrences causally related to treatment / all | 1 / 11            | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1           |  |
| Pneumonia influenzal                            |                   |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0           |  |
| Pneumonia klebsiella                            |                   |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%)  | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Pneumonia pneumococcal                          |                   |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%)  | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1           |  |
| Respiratory tract infection                     |                   |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sepsis  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 1 / 2           |  |
| Skin bacterial infection                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal bacteraemia                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal infection                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Streptococcal infection                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tracheobronchitis                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary tract infection                         |                  |                 |  |
| subjects affected / exposed                     | 3 / 1729 (0.17%) | 4 / 894 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urosepsis                                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Metabolism and nutrition disorders              |                  |                 |  |
| Dehydration                                     |                  |                 |  |
| subjects affected / exposed                     | 2 / 1729 (0.12%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetic ketoacidosis                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gout  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperammonaemia                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperkalaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 0 / 894 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypoglycaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1729 (0.06%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Hypokalaemia                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 2 / 894 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Type 2 diabetes mellitus                        |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1729 (0.00%) | 1 / 894 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 1.5 %

| <b>Non-serious adverse events</b>                     | Serelaxin + SOC     | Standard of Care   |  |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                     |                    |  |
| subjects affected / exposed                           | 637 / 1729 (36.84%) | 324 / 894 (36.24%) |  |
| Investigations  |                     |                    |  |
| Blood pressure systolic decreased                     |                     |                    |  |
| subjects affected / exposed                           | 49 / 1729 (2.83%)   | 2 / 894 (0.22%)    |  |
| occurrences (all)                                     | 51                  | 2                  |  |
| Vascular disorders                                    |                     |                    |  |
| Hypotension   |                     |                    |  |
| subjects affected / exposed                           | 48 / 1729 (2.78%)   | 18 / 894 (2.01%)   |  |
| occurrences (all)                                     | 49                  | 18                 |  |
| Cardiac disorders                                     |                     |                    |  |
| Atrial fibrillation                                   |                     |                    |  |
| subjects affected / exposed                           | 34 / 1729 (1.97%)   | 23 / 894 (2.57%)   |  |
| occurrences (all)                                     | 34                  | 23                 |  |
| Cardiac failure                                       |                     |                    |  |
| subjects affected / exposed                           | 81 / 1729 (4.68%)   | 56 / 894 (6.26%)   |  |
| occurrences (all)                                     | 85                  | 58                 |  |
| Mitral valve incompetence                             |                     |                    |  |
| subjects affected / exposed                           | 28 / 1729 (1.62%)   | 12 / 894 (1.34%)   |  |
| occurrences (all)                                     | 28                  | 12                 |  |
| Nervous system disorders                              |                     |                    |  |
| Headache  |                     |                    |  |
| subjects affected / exposed                           | 45 / 1729 (2.60%)   | 18 / 894 (2.01%)   |  |
| occurrences (all)                                     | 45                  | 18                 |  |
| Blood and lymphatic system disorders                  |                     |                    |  |
| Anaemia   |                     |                    |  |
| subjects affected / exposed                           | 49 / 1729 (2.83%)   | 9 / 894 (1.01%)    |  |
| occurrences (all)                                     | 49                  | 9                  |  |
| General disorders and administration site conditions  |                     |                    |  |

|  |                         |                        |  |
|--|-------------------------|------------------------|--|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)          | 24 / 1729 (1.39%)<br>24 | 21 / 894 (2.35%)<br>21 |  |
| Gastrointestinal disorders   |                         |                        |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)     | 74 / 1729 (4.28%)<br>74 | 32 / 894 (3.58%)<br>32 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)        | 29 / 1729 (1.68%)<br>29 | 21 / 894 (2.35%)<br>21 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)           | 40 / 1729 (2.31%)<br>40 | 17 / 894 (1.90%)<br>17 |  |
| Psychiatric disorders  |                         |                        |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)          | 27 / 1729 (1.56%)<br>28 | 16 / 894 (1.79%)<br>16 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)         | 58 / 1729 (3.35%)<br>58 | 21 / 894 (2.35%)<br>21 |  |
| Renal and urinary disorders  |                         |                        |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)    | 18 / 1729 (1.04%)<br>18 | 18 / 894 (2.01%)<br>18 |  |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all) | 30 / 1729 (1.74%)<br>30 | 18 / 894 (2.01%)<br>18 |  |
| Musculoskeletal and connective tissue disorders                      |                         |                        |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)        | 28 / 1729 (1.62%)<br>28 | 11 / 894 (1.23%)<br>11 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)    | 33 / 1729 (1.91%)<br>33 | 8 / 894 (0.89%)<br>8   |  |
| Infections and infestations  |                         |                        |  |

|                                    |                    |                  |  |
|------------------------------------|--------------------|------------------|--|
| Bronchitis                         |                    |                  |  |
| subjects affected / exposed        | 24 / 1729 (1.39%)  | 14 / 894 (1.57%) |  |
| occurrences (all)                  | 24                 | 14               |  |
| Urinary tract infection            |                    |                  |  |
| subjects affected / exposed        | 56 / 1729 (3.24%)  | 26 / 894 (2.91%) |  |
| occurrences (all)                  | 56                 | 26               |  |
| Metabolism and nutrition disorders |                    |                  |  |
| Hyperuricaemia                     |                    |                  |  |
| subjects affected / exposed        | 47 / 1729 (2.72%)  | 35 / 894 (3.91%) |  |
| occurrences (all)                  | 47                 | 35               |  |
| Hypokalaemia                       |                    |                  |  |
| subjects affected / exposed        | 119 / 1729 (6.88%) | 73 / 894 (8.17%) |  |
| occurrences (all)                  | 120                | 74               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 14 February 2013 | Amendment 1 was initiated at the request of German Health Authorities and was applicable only to German sites participating in this trial. As part of the review process, German health authorities requested to amend the protocol with inclusion of the following 2 requirements:<br>1. As part of additional safety measures and to avoid any potential risk of hypotension with the infusion of serelaxin, it was recommended to clarify the use of an infusion pump, a drip or any other controllable infusion systems to ensure a constant infusion rate of serelaxin at 10ml/hour.<br>2. To further clarify the informed consent procedure related to the nature of the witness, an "independent second physician or nurse" was added who will co-sign the ICF and thereby confirm that the patient provided informed consent according to his/her own will following receipt of all study related information based on his/her ability to understand the trial procedures. |
| 19 June 2014     | Amendment 2 was introduced based on the initial feedback gathered from the investigators already screening and recruiting patients, the request for clarification from some local health authorities, and further discussions with the Executive Committee Board. These changes aimed at further strengthening the protocol, facilitating recruitment and ensuring possible data merging with other serelaxin studies like RELAX-AHF-2.  |
| 24 June 2015     | Amendment 3: AHF is a complex and subjective clinical diagnosis. Since the diagnosis of AHF is primarily based on clinical observations that are interpreted bedside, in an urgent care environment, based on the clinical judgment of the investigator, the diagnosis is sometimes difficult to qualify. Therefore, the study Executive Committee recommended changes to better specify the criteria defining AHF in the patient population under investigation, correct inconsistencies and improve the overall clarity of the study.  |
| 19 October 2016  | Amendment 4 was introduced since the Executive Committee recommended during its meeting held on 15th of June 2016 to increase the number of randomized patients from 2,685 to 3,183.<br>The rationale for the increase was that the number of events constitutive of the primary endpoint was lower than expected.<br>This decision was endorsed by the Data Monitoring Committee (DMC).   |

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.

This study was terminated early following the neutral results from the Phase III RELAX-AHF-2 (CRLX030A2301) study which did not support further development of serelaxin in AHF.

Notes: