



## Clinical trial results:

**A multicenter, randomized, open label, parallel group study comparing pre-discharge and post-discharge treatment initiation with LCZ696 in heart failure patients with reduced ejection-fraction hospitalized for an acute decompensation event (ADHF) (the TRANSITION study)**

### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2015-003266-87                      |
| Trial protocol           | DE GB SK PT SE ES CZ FR BE PL HU IT |
| Global end of trial date | 20 June 2018                        |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 06 July 2019 |
| First version publication date | 06 July 2019 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLCZ696B2401 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02661217 |
| 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                       | 20 June 2018 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 20 June 2018 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the proportion of subjects in the pre-discharge and post-discharge treatment initiation groups achieving the target dose of 200 mg LCZ696 bid at the end of the Week 10 after randomization (treatment epoch), regardless of previous temporary dose interruption or down-titration.

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                          | 12 February 2016 |
| 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 | Lebanon: 33            |
| Country: Number of subjects enrolled | Saudi Arabia: 7        |
| Country: Number of subjects enrolled | Turkey: 43             |
| Country: Number of subjects enrolled | Belgium: 29            |
| Country: Number of subjects enrolled | France: 20             |
| Country: Number of subjects enrolled | Germany: 129           |
| Country: Number of subjects enrolled | Italy: 30              |
| Country: Number of subjects enrolled | Norway: 30             |
| Country: Number of subjects enrolled | Portugal: 51           |
| Country: Number of subjects enrolled | Spain: 147             |
| Country: Number of subjects enrolled | Sweden: 5              |
| Country: Number of subjects enrolled | Switzerland: 21        |
| Country: Number of subjects enrolled | United Kingdom: 88     |
| Country: Number of subjects enrolled | Czech Republic: 78     |
| Country: Number of subjects enrolled | Poland: 104            |
| Country: Number of subjects enrolled | Russian Federation: 74 |
| Country: Number of subjects enrolled | Slovakia: 57           |
| Country: Number of subjects enrolled | Argentina: 37          |

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Canada: 19 |
| Worldwide total number of subjects   | 1002       |
| EEA total number of subjects         | 768        |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 392 |
| From 65 to 84 years                       | 570 |
| 85 years and over                         | 40  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 1002 patients were randomized, including 2 screen failure patients (1 in each group) and 2 patients who were randomized in error. A total of 998 patients entered the 10 week treatment epoch: 497 patients in pre-discharge group and 501 patients in post-discharged group.

### Pre-assignment

Screening details:

The study consisted of 3 Epochs: the Screening Epoch (from signing of informed consent form to randomization), the treatment epoch (10 weeks following randomization), and a 16 weeks Follow-up Epoch following treatment epoch.

### 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>             | LCZ696 Pre-discharge treatment initiation |

Arm description:

Patients received first dose at any point after Randomization but no later than 12 h before discharge.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | LCZ696       |
| Investigational medicinal product code | LCZ696       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects were required to take the study medication bid in addition to their daily therapies, possibly at 12 hour interval (i.e., at 7:00 am in the morning and 7:00 pm in the evening). Tablets were taken with a glass of water, and were administered with or without food.

|                  |  |
|------------------|--|
| <b>Arm title</b> | LCZ696 Post-discharge treatment initiation |
|------------------|--|

Arm description:

Patients received first dose after discharge and up to 14 days thereafter.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | LCZ696       |
| Investigational medicinal product code | LCZ696       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects were required to take the study medication bid in addition to their daily therapies, possibly at 12 hour interval (i.e., at 7:00 am in the morning and 7:00 pm in the evening). Tablets were taken with a glass of water, and were administered with or without food.

| <b>Number of subjects in period 1</b> | <b>LCZ696 Pre-discharge treatment initiation</b> | <b>LCZ696 Post-discharge treatment initiation</b> |
|---------------------------------------|--|---|
| Started                               | 500  | 502   |
| 10 weeks treatment epoch              | 460  | 455   |
| Completed                             | 425  | 419   |
| Not completed                         | 75   | 83  |
| Adverse event, serious fatal          | 22   | 17  |
| Physician decision                    | 12   | 15  |
| Consent withdrawn by subject          | 15   | 19  |
| Adverse event, non-fatal              | 10   | 8   |
| Protocol Deviation                    | -  | 4   |
| Non-compliance with study treatment   | 5  | 5   |
| Did not enter follow-up epoch         | 7  | 10  |
| Mis-randomized and not treated        | 3  | 1   |
| Lost to follow-up                     | 1  | 4   |

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | LCZ696 Pre-discharge treatment initiation  |
| Reporting group description:   |  |
| Patients received first dose at any point after Randomization but no later than 12 h before discharge. |  |
| Reporting group title  | LCZ696 Post-discharge treatment initiation |
| Reporting group description:   |  |
| Patients received first dose after discharge and up to 14 days thereafter.                             |  |

| Reporting group values                             | LCZ696 Pre-discharge treatment initiation | LCZ696 Post-discharge treatment initiation | Total |
|--|---|--|-------|
| Number of subjects                                 | 500                                       | 502  | 1002  |
| 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)                               | 206                                       | 186  | 392   |
| From 65-84 years                                   | 275                                       | 295  | 570   |
| 85 years and over                                  | 19  | 21   | 40    |
| Age Continuous                                     |   |  |       |
| Units: years                                       |   |  |       |
| arithmetic mean                                    | 66.7                                      | 67.0                                       |       |
| standard deviation                                 | ± 12.27                                   | ± 11.67                                    | -     |
| Sex: Female, Male                                  |   |  |       |
| Units: Subjects                                    |   |  |       |
| Female   | 126                                       | 125  | 251   |
| Male   | 374                                       | 377  | 751   |
| Race/Ethnicity, Customized                         |   |  |       |
| Units: Subjects                                    |   |  |       |
| Caucasian  | 488                                       | 486  | 974   |
| Black  | 5   | 8  | 13    |
| Asian  | 7   | 3  | 10    |
| Native American                                    | 0   | 1  | 1     |
| Pacific Islander                                   | 0   | 1  | 1     |
| Other  | 0   | 1  | 1     |
| Unknown  | 0   | 2  | 2     |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | LCZ696 Pre-discharge treatment initiation  |
| Reporting group description:   |  |
| Patients received first dose at any point after Randomization but no later than 12 h before discharge. |  |
| Reporting group title  | LCZ696 Post-discharge treatment initiation |
| Reporting group description:   |  |
| Patients received first dose after discharge and up to 14 days thereafter.                             |  |

### Primary: Percentage of patients achieving the target dose of LCZ696 200 mg bid at 10 weeks post randomization

|  |  |
|--|--|
| End point title  | Percentage of patients achieving the target dose of LCZ696 200 mg bid at 10 weeks post randomization |
| End point description:   |  |
| Percentage of patients achieving and maintaining LCZ696 200 mg bid for at least 2 weeks leading to Week 10 |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| 10 weeks after Randomization   |  |

| End point values            | LCZ696 Pre-discharge treatment initiation | LCZ696 Post-discharge treatment initiation |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                            |  |  |
| Number of subjects analysed | 493                                       | 489  |  |  |
| Units: Participants         | 224                                       | 248  |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of subjects achieving 200 mg at 10 weeks                                      |
| Comparison groups                       | LCZ696 Post-discharge treatment initiation v LCZ696 Pre-discharge treatment initiation |
| Number of subjects included in analysis | 982  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.099  |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Risk ratio (RR)  |
| Point estimate                          | 0.896  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.786   |
| upper limit         | 1.021   |

### Secondary: Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid

|   |   |
|---|---|
| End point title   | Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid |
| End point description:<br>Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid for at least 2 weeks leading to Week 10 |   |
| End point type  | Secondary   |
| End point timeframe:<br>10 weeks after Randomization  |   |

| End point values            | LCZ696 Pre-discharge treatment initiation | LCZ696 Post-discharge treatment initiation |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                            |  |  |
| Number of subjects analysed | 493                                       | 489  |  |  |
| Units: Participants         | 306                                       | 335  |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Subjects maintaining 100 and/or 200 mg   |
| Comparison groups                       | LCZ696 Pre-discharge treatment initiation v LCZ696 Post-discharge treatment initiation |
| Number of subjects included in analysis | 982  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.034  |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Risk ratio (RR)  |
| Point estimate                          | 0.906  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.827  |
| upper limit                             | 0.993  |



**Secondary: Percentage of patients achieving and maintaining any dose of LCZ696**

|   |   |
|---|---|
| End point title   | Percentage of patients achieving and maintaining any dose of LCZ696 |
| End point description:<br>Percentage of patients achieving any dose of LCZ696 for at least 2 weeks leading to 10 weeks of treatment |   |
| End point type  | Secondary   |
| End point timeframe:<br>10 weeks after Randomization  |   |

| End point values            | LCZ696 Pre-discharge treatment initiation | LCZ696 Post-discharge treatment initiation |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                            |  |  |
| Number of subjects analysed | 493                                       | 489  |  |  |
| Units: Participants         | 424                                       | 438  |  |  |

**Statistical analyses**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Subjects maintaining any dose  |
| Comparison groups                       | LCZ696 Pre-discharge treatment initiation v LCZ696 Post-discharge treatment initiation |
| Number of subjects included in analysis | 982  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.089  |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Risk ratio (RR)  |
| Point estimate                          | 0.96   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.916  |
| upper limit                             | 1.006  |

**Secondary: Percentage of patients permanently discontinued from treatment**

|  |  |
|--|--|
| End point title  | Percentage of patients permanently discontinued from treatment |
| End point description:<br>Percentage of patients permanently discontinued from LCZ696 (1) up to week 10 due to AEs, and (2) up to week 26 due to any reasons |  |
| End point type   | Secondary  |
| End point timeframe:<br>10 weeks after Randomization AND 26 weeks after randomization  |  |

| <b>End point values</b>          | LCZ696 Pre-discharge treatment initiation | LCZ696 Post-discharge treatment initiation |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                           | Reporting group                            |  |  |
| Number of subjects analysed      | 493                                       | 489  |  |  |
| Units: Participants              |   |  |  |  |
| up to week 10 due to AEs         | 36  | 24   |  |  |
| up to week 26 due to any reasons | 83  | 78   |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

26 weeks after randomization

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | LCZ696 Pre-discharge treatment initiation |
|-----------------------|---|

Reporting group description:

Patients received first dose at any point after Randomization but no later than 12 h before discharge.

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description:

All patients

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | LCZ696 Post-discharge treatment |
|-----------------------|---------------------------------|

Reporting group description:

Patients received first dose after discharge and up to 14 days thereafter.

| Serious adverse events  | LCZ696 Pre-discharge treatment initiation | All patients       | LCZ696 Post-discharge treatment |
|---|---|--------------------|---------------------------------|
| Total subjects affected by serious adverse events                   |   |                    |                                 |
| subjects affected / exposed   | 159 / 493 (32.25%)                        | 293 / 982 (29.84%) | 134 / 489 (27.40%)              |
| number of deaths (all causes)                                       | 23  | 36                 | 13                              |
| number of deaths resulting from adverse events                      | 0   | 0                  | 0                               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                    |                                 |
| Adenocarcinoma gastric  |   |                    |                                 |
| subjects affected / exposed   | 0 / 493 (0.00%)                           | 1 / 982 (0.10%)    | 1 / 489 (0.20%)                 |
| occurrences causally related to treatment / all                     | 0 / 0                                     | 0 / 1              | 0 / 1                           |
| deaths causally related to treatment / all                          | 0 / 0                                     | 0 / 0              | 0 / 0                           |
| Brain neoplasm  |   |                    |                                 |
| subjects affected / exposed   | 1 / 493 (0.20%)                           | 1 / 982 (0.10%)    | 0 / 489 (0.00%)                 |
| occurrences causally related to treatment / all                     | 1 / 1                                     | 1 / 1              | 0 / 0                           |
| deaths causally related to treatment / all                          | 0 / 0                                     | 0 / 0              | 0 / 0                           |
| Breast cancer   |   |                    |                                 |
| subjects affected / exposed   | 2 / 493 (0.41%)                           | 2 / 982 (0.20%)    | 0 / 489 (0.00%)                 |
| occurrences causally related to treatment / all                     | 0 / 2                                     | 0 / 2              | 0 / 0                           |
| deaths causally related to treatment / all                          | 0 / 0                                     | 0 / 0              | 0 / 0                           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Lung neoplasm malignant<br>subjects affected / exposed | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to<br>treatment / all     | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant neoplasm of ampulla of<br>Vater              |                 |                 |                 |
| subjects affected / exposed                            | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant peritoneal neoplasm                          |                 |                 |                 |
| subjects affected / exposed                            | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to liver                                    |                 |                 |                 |
| subjects affected / exposed                            | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to lung                                     |                 |                 |                 |
| subjects affected / exposed                            | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal adenocarcinoma                                  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Transitional cell carcinoma                            |                 |                 |                 |
| subjects affected / exposed                            | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                     |                 |                 |                 |
| Aortic aneurysm  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to<br>treatment / all     | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 6 / 493 (1.22%) | 8 / 982 (0.81%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all      | 2 / 5           | 4 / 7           | 2 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral arterial occlusive disease                |                 |                 |                 |
| subjects affected / exposed                          | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral vascular disorder                         |                 |                 |                 |
| subjects affected / exposed                          | 2 / 493 (0.41%) | 2 / 982 (0.20%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Impaired healing                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 2 / 493 (0.41%) | 7 / 982 (0.71%) | 5 / 489 (1.02%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 7           | 0 / 5           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Oedema peripheral                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 4 / 982 (0.41%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 5           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden cardiac death                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Sudden death                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 2 / 982 (0.20%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Benign prostatic hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute pulmonary oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Asthma  |                 |                 |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                  |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 7 / 982 (0.71%)  | 4 / 489 (0.82%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6            | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Cough   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Dyspnoea  |                 |                  |                 |
| subjects affected / exposed                     | 6 / 493 (1.22%) | 11 / 982 (1.12%) | 5 / 489 (1.02%) |
| occurrences causally related to treatment / all | 1 / 6           | 3 / 14           | 2 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Haemoptysis                                     |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Mediastinal haematoma                           |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Orthopnoea                                      |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pleural effusion                                |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pulmonary congestion                            |                 |                  |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pulmonary embolism                              |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pulmonary oedema                                |                 |                  |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 10 / 982 (1.02%) | 7 / 489 (1.43%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 10           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            | 0 / 0           |
| Respiratory failure                             |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Psychiatric disorders                           |                 |                  |                 |
| Insomnia  |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Product issues                                  |                 |                  |                 |
| Device battery issue                            |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Device dislocation                              |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Investigations                                  |                 |                  |                 |
| Blood creatinine increased                      |                 |                  |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 2 / 982 (0.20%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 2 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiac output decreased                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ejection fraction abnormal                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ejection fraction decreased                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 2 / 982 (0.20%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical condition abnormal             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Heart rate abnormal                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic enzyme abnormal                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic enzyme increased                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| International normalised ratio increased        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight increased                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Craniocerebral injury                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple injuries                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Patella fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural haematoma                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transplant failure                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Tracheo-oesophageal fistula                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 4 / 982 (0.41%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 3 / 982 (0.31%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 3 / 982 (0.31%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 3 / 982 (0.31%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Arteriosclerosis coronary artery                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 2 / 982 (0.20%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 4 / 493 (0.81%) | 9 / 982 (0.92%) | 5 / 489 (1.02%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 10          | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial tachycardia                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block complete                 |                 |                 |                 |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 493 (0.41%)  | 4 / 982 (0.41%)  | 2 / 489 (0.41%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bradycardia                                     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 493 (0.41%)  | 3 / 982 (0.31%)  | 1 / 489 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac arrest                                  |                  |                  |                  |
| subjects affected / exposed                     | 4 / 493 (0.81%)  | 5 / 982 (0.51%)  | 1 / 489 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 4            | 0 / 1            |
| Cardiac failure                                 |                  |                  |                  |
| subjects affected / exposed                     | 46 / 493 (9.33%) | 91 / 982 (9.27%) | 45 / 489 (9.20%) |
| occurrences causally related to treatment / all | 0 / 59           | 2 / 100          | 2 / 41           |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 6            | 0 / 2            |
| Cardiac failure acute                           |                  |                  |                  |
| subjects affected / exposed                     | 11 / 493 (2.23%) | 20 / 982 (2.04%) | 9 / 489 (1.84%)  |
| occurrences causally related to treatment / all | 0 / 13           | 1 / 20           | 1 / 7            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| Cardiac failure chronic                         |                  |                  |                  |
| subjects affected / exposed                     | 3 / 493 (0.61%)  | 5 / 982 (0.51%)  | 2 / 489 (0.41%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| Cardiac failure congestive                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 493 (0.20%)  | 5 / 982 (0.51%)  | 4 / 489 (0.82%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardio-respiratory arrest                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 493 (0.20%)  | 3 / 982 (0.31%)  | 2 / 489 (0.41%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            | 0 / 1            |
| Cardiogenic shock                               |                  |                  |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 6 / 982 (0.61%) | 5 / 489 (1.02%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 1           |
| Cardiomyopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congestive cardiomyopathy                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 2 / 982 (0.20%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Left ventricular failure                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Low cardiac output syndrome                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial fibrosis                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 2 / 982 (0.20%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus arrest                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular arrhythmia                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular extrasystoles                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular fibrillation                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 5 / 982 (0.51%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Aphasia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Autonomic nervous system imbalance              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain injury                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral arteriosclerosis                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral ischaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 2           |
| Cognitive disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Extrapyramidal disorder                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxic-ischaemic encephalopathy                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 2 / 982 (0.20%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 6 / 982 (0.61%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 2 / 3           | 3 / 6           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%) | 5 / 982 (0.51%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypocoagulable state                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukocytosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Splenic haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 3 / 982 (0.31%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea haemorrhagic                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal inflammation                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal haemorrhage                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lip swelling                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subileus  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Acute hepatic failure                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 2 / 982 (0.20%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Hepatic function abnormal                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperbilirubinaemia                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jaundice cholestatic                            |                 |                 |                 |

|   |                  |                  |                 |
|---|------------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%)  | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                  |                  |                 |
| Diabetic foot                                   |                  |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%)  | 3 / 982 (0.31%)  | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0           |
| Skin ulcer                                      |                  |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%)  | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Renal and urinary disorders                     |                  |                  |                 |
| Acute kidney injury                             |                  |                  |                 |
| subjects affected / exposed                     | 12 / 493 (2.43%) | 19 / 982 (1.93%) | 7 / 489 (1.43%) |
| occurrences causally related to treatment / all | 4 / 10           | 5 / 15           | 1 / 5           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1           |
| Chronic kidney disease                          |                  |                  |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%)  | 5 / 982 (0.51%)  | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 4            | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Haematuria                                      |                  |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%)  | 2 / 982 (0.20%)  | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Renal failure                                   |                  |                  |                 |
| subjects affected / exposed                     | 3 / 493 (0.61%)  | 7 / 982 (0.71%)  | 4 / 489 (0.82%) |
| occurrences causally related to treatment / all | 3 / 3            | 4 / 5            | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Renal impairment                                |                  |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%)  | 4 / 982 (0.41%)  | 4 / 489 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 3            | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Endocrine disorders                             |                  |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Hypothyroidism                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fistula   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal pain                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myalgia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| Infections and infestations<br>Bacterial sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 493 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 1<br>0 / 1 | 1 / 489 (0.20%)<br>0 / 1<br>0 / 1 |
| Biliary sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | 0 / 493 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 1<br>0 / 0 | 1 / 489 (0.20%)<br>0 / 1<br>0 / 0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                      | 1 / 493 (0.20%)<br>0 / 1<br>0 / 0 | 5 / 982 (0.51%)<br>0 / 5<br>0 / 1 | 4 / 489 (0.82%)<br>0 / 4<br>0 / 1 |
| Catheter site abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | 0 / 493 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 1<br>0 / 0 | 1 / 489 (0.20%)<br>0 / 1<br>0 / 0 |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                      | 1 / 493 (0.20%)<br>0 / 1<br>0 / 0 | 2 / 982 (0.20%)<br>0 / 2<br>0 / 0 | 1 / 489 (0.20%)<br>0 / 1<br>0 / 0 |
| Device related infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                        | 1 / 493 (0.20%)<br>0 / 1<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 1<br>0 / 0 | 0 / 489 (0.00%)<br>0 / 0<br>0 / 0 |
| Diarrhoea infectious<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                            | 1 / 493 (0.20%)<br>0 / 1<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 1<br>0 / 0 | 0 / 489 (0.00%)<br>0 / 0<br>0 / 0 |
| Endocarditis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                    | 0 / 493 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 982 (0.10%)<br>0 / 0<br>0 / 0 | 1 / 489 (0.20%)<br>0 / 0<br>0 / 0 |
| Epididymitis  |                                   |                                   |                                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 4 / 982 (0.41%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gangrene  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 2 / 982 (0.20%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 4 / 982 (0.41%) | 3 / 489 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection viral         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung infection                                  |                 |                 |                 |



|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Pneumonia                                       |                 |                  |                 |
| subjects affected / exposed                     | 7 / 493 (1.42%) | 15 / 982 (1.53%) | 8 / 489 (1.64%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 12           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Postoperative wound infection                   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Q fever   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Respiratory tract infection                     |                 |                  |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 4 / 982 (0.41%)  | 4 / 489 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Sepsis  |                 |                  |                 |
| subjects affected / exposed                     | 2 / 493 (0.41%) | 3 / 982 (0.31%)  | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 1           |
| Septic phlebitis                                |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%)  | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Septic shock                                    |                 |                  |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%)  | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 1           |
| Tuberculosis                                    |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 4 / 493 (0.81%) | 6 / 982 (0.61%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes mellitus inadequate control            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fluid overload                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gout  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 1 / 982 (0.10%) | 0 / 489 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 493 (0.61%) | 9 / 982 (0.92%) | 6 / 489 (1.23%) |
| occurrences causally related to treatment / all | 2 / 2           | 6 / 8           | 4 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 493 (0.00%) | 1 / 982 (0.10%) | 1 / 489 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 493 (0.20%) | 3 / 982 (0.31%) | 2 / 489 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | LCZ696 Pre-discharge treatment initiation | All patients       | LCZ696 Post-discharge treatment |
|---|---|--------------------|---------------------------------|
| Total subjects affected by non-serious adverse events |   |                    |                                 |
| subjects affected / exposed                           | 200 / 493 (40.57%)                        | 401 / 982 (40.84%) | 201 / 489 (41.10%)              |
| Vascular disorders                                    |   |                    |                                 |
| Hypotension   |   |                    |                                 |
| subjects affected / exposed                           | 71 / 493 (14.40%)                         | 138 / 982 (14.05%) | 67 / 489 (13.70%)               |
| occurrences (all)                                     | 74  | 145                | 71                              |
| Nervous system disorders                              |   |                    |                                 |
| Dizziness   |   |                    |                                 |
| subjects affected / exposed                           | 32 / 493 (6.49%)                          | 62 / 982 (6.31%)   | 30 / 489 (6.13%)                |
| occurrences (all)                                     | 32  | 63                 | 31                              |
| General disorders and administration site conditions  |   |                    |                                 |
| Oedema peripheral                                     |   |                    |                                 |
| subjects affected / exposed                           | 20 / 493 (4.06%)                          | 46 / 982 (4.68%)   | 26 / 489 (5.32%)                |
| occurrences (all)                                     | 19  | 48                 | 29                              |
| Gastrointestinal disorders                            |   |                    |                                 |
| Diarrhoea   |   |                    |                                 |
| subjects affected / exposed                           | 17 / 493 (3.45%)                          | 46 / 982 (4.68%)   | 29 / 489 (5.93%)                |
| occurrences (all)                                     | 18  | 47                 | 29                              |
| Renal and urinary disorders                           |   |                    |                                 |

|  |                         |                           |                         |
|--|-------------------------|---------------------------|-------------------------|
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)                                       | 36 / 493 (7.30%)<br>44  | 60 / 982 (6.11%)<br>68    | 24 / 489 (4.91%)<br>24  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 29 / 493 (5.88%)<br>35  | 48 / 982 (4.89%)<br>49    | 19 / 489 (3.89%)<br>14  |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)    | 67 / 493 (13.59%)<br>80 | 126 / 982 (12.83%)<br>153 | 59 / 489 (12.07%)<br>73 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 04 February 2016 | The purpose of this amendment was to address the inquiry by the Health Authorities from Germany. This change applied to Germany only referring to the eligibility of subjects. |
| 18 July 2016     | Wording changes + clarifications   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported