



Clinical trial results:

A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

Summary

| | |
|--------------------------|--|
| EudraCT number | 2013-001498-25 |
| Trial protocol | SK BE SE IE BG HU PT LT IT CZ AT EE DK ES LV NL GR GB PL |
| Global end of trial date | NO 01 February 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 28 April 2018 |
| First version publication date | 07 February 2018 |

| | |
|-------------------------|---|
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set The titles of end points 1, 2, 3 and 5 have been updated. |
|-------------------------|---|

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRLX030A2301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01870778 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 February 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 February 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were:

- To demonstrate that serelaxin was superior to placebo in reducing cardiovascular (CV) death in acute heart failure (AHF) patients during a follow-up period of 180 days.
- To demonstrate that serelaxin was superior to placebo in reducing worsening heart failure (WHF) through Day 5.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 02 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Australia: 45 |
| Country: Number of subjects enrolled | Argentina: 493 |
| Country: Number of subjects enrolled | Austria: 72 |
| Country: Number of subjects enrolled | Belgium: 53 |
| Country: Number of subjects enrolled | Brazil: 87 |
| Country: Number of subjects enrolled | Bulgaria: 472 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Chile: 6 |
| Country: Number of subjects enrolled | Colombia: 9 |
| Country: Number of subjects enrolled | Czech Republic: 413 |
| Country: Number of subjects enrolled | Denmark: 18 |
| Country: Number of subjects enrolled | France: 138 |
| Country: Number of subjects enrolled | Germany: 641 |
| Country: Number of subjects enrolled | United Kingdom: 138 |
| Country: Number of subjects enrolled | Greece: 97 |
| Country: Number of subjects enrolled | Hungary: 351 |
| Country: Number of subjects enrolled | Ireland: 18 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Israel: 256 |
| Country: Number of subjects enrolled | Italy: 266 |
| Country: Number of subjects enrolled | Mexico: 46 |
| Country: Number of subjects enrolled | Netherlands: 150 |
| Country: Number of subjects enrolled | Peru: 1 |
| Country: Number of subjects enrolled | Poland: 450 |
| Country: Number of subjects enrolled | Portugal: 59 |
| Country: Number of subjects enrolled | Romania: 466 |
| Country: Number of subjects enrolled | Russian Federation: 420 |
| Country: Number of subjects enrolled | Slovakia: 258 |
| Country: Number of subjects enrolled | South Africa: 30 |
| Country: Number of subjects enrolled | Spain: 239 |
| Country: Number of subjects enrolled | Sweden: 27 |
| Country: Number of subjects enrolled | Switzerland: 42 |
| Country: Number of subjects enrolled | Turkey: 88 |
| Country: Number of subjects enrolled | United States: 687 |
| Worldwide total number of subjects | 6545 |
| EEA total number of subjects | 4326 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1411 |
| From 65 to 84 years | 4210 |
| 85 years and over | 924 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to Serelaxin or matching placebo.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

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

| | |
|------------------|--------------------|
| Arm title | Serelaxin (RLX030) |
|------------------|--------------------|

Arm description:

Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.

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

Dosage and administration details:

Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.

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

Dosage and administration details:

Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.

| Number of subjects in period 1 | Serelaxin (RLX030) | Placebo |
|---------------------------------------|---------------------|---------------------|
| Started | 3274 | 3271 |
| Safety set | 3257 ^[1] | 3248 ^[2] |
| Full analysis set | 3274 | 3271 |
| Biomarker analysis set | 521 ^[3] | 510 ^[4] |

| | | |
|------------------------------|------|------|
| Completed | 3266 | 3262 |
| Not completed | 8 | 9 |
| Consent withdrawn by subject | 8 | 7 |
| Lost to follow-up | - | 2 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The numbers are correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The numbers are correct.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The numbers are correct.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The numbers are correct.

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Serelaxin (RLX030) |
| Reporting group description: | |
| Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours. | |

| Reporting group values | Serelaxin (RLX030) | Placebo | Total |
|---|--------------------|---------|-------|
| Number of subjects | 3274 | 3271 | 6545 |
| 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) | 686 | 725 | 1411 |
| From 65-84 years | 2106 | 2104 | 4210 |
| 85 years and over | 482 | 442 | 924 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 73.1 | 72.8 | |
| standard deviation | ± 11.24 | ± 11.17 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 1296 | 1341 | 2637 |
| Male | 1978 | 1930 | 3908 |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Serelaxin (RLX030) |
| Reporting group description: Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours. | |

Primary: Percentage of participants with confirmed cardiovascular (CV) death through day 180

| | |
|---|---|
| End point title | Percentage of participants with confirmed cardiovascular (CV) death through day 180 |
| End point description: The percentage of participants with an adjudicated CV death through day 180 was assessed. | |
| End point type | Primary |
| End point timeframe: 180 days | |

| End point values | Serelaxin (RLX030) | Placebo | | |
|-----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 8.7 | 8.9 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Time to confirmed CV death |
| Comparison groups | Placebo v Serelaxin (RLX030) |
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3857 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.15 |

Notes:

[1] - Adjusted alpha p-value based on multiple testing procedure.

Primary: Percentage of participants with worsening of heart failure (WHF) through day 5

| | |
|-----------------|--|
| End point title | Percentage of participants with worsening of heart failure (WHF) through day 5 |
|-----------------|--|

End point description:

The percentage of participants with WHF through day 5 was assessed.

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

End point timeframe:

Day 5

| End point values | Serelaxin (RLX030) | Placebo | | |
|-----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 6.9 | 7.7 | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Time to WHF |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0968 ^[2] |
| Method | Gehan's generalized Wilcoxon test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.07 |

Notes:

[2] - Adjusted p-value based on multiple testing procedure

Secondary: Percentage of participants with all-cause death through day 180

| | |
|-----------------|---|
| End point title | Percentage of participants with all-cause death through day 180 |
|-----------------|---|

End point description:

The percentage of participants with all-cause death through day 180 was assessed.

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

End point timeframe:

180 days

| End point values | Serelaxin (RLX030) | Placebo | | |
|-----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 11.2 | 11.9 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Time to all cause death |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.389 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.08 |

Secondary: Length of total hospital stay (LOS) during the index acute heart failure (AHF) hospitalization

| | |
|--|--|
| End point title | Length of total hospital stay (LOS) during the index acute heart failure (AHF) hospitalization |
| End point description: | |
| Length of stay was defined as the index hospitalization discharge date and time minus the baseline date and time plus 1 day. | |
| End point type | Secondary |
| End point timeframe: | |
| 180 days (Participants still in the hospital at Day 60 were censored at Day 60) | |

| End point values | Serelaxin (RLX030) | Placebo | | |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 9.362 (\pm 9.3581) | 9.545 (\pm 9.6739) | | |

Statistical analyses

| Statistical analysis title | LOS during the index AHF hospitalization |
|---|--|
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2204 ^[3] |
| Method | Wilcoxon rank sum test |

Notes:

[3] - Based on multiple testing procedure

Secondary: Percentage of participants with first occurrence of adjudicated CV death or adjudicated re-hospitalization

| End point title | Percentage of participants with first occurrence of adjudicated CV death or adjudicated re-hospitalization |
|------------------------|--|
| End point description: | The percentage of participants with adjudicated CV death or adjudicated re-hospitalization through day 180 was assessed. |
| End point type | Secondary |
| End point timeframe: | 180 days |

| End point values | Serelaxin (RLX030) | Placebo | | |
|-----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 24.3 | 24.9 | | |

Statistical analyses

| Statistical analysis title | Time to 1st occ. of adj. CV death or adj. re-hosp. |
|----------------------------|--|
| Comparison groups | Serelaxin (RLX030) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2744 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.07 |

Notes:

[4] - Adjusted p-value based on multiple testing procedure

Secondary: Length of Intensive Care Unit (ICU) and/or Coronary care unit (CCU) stay for the index AHF hospitalization

| | |
|-----------------|--|
| End point title | Length of Intensive Care Unit (ICU) and/or Coronary care unit (CCU) stay for the index AHF hospitalization |
|-----------------|--|

End point description:

Length of stay was defined as the hospitalization discharge date and the time minus the baseline date and time plus 1 day.

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

End point timeframe:

180 days (Patients still in the hospital at Day 60 were censored at Day 60)

| End point values | Serelaxin (RLX030) | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3274 | 3271 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 3.8 (± 8.29) | 4.1 (± 8.77) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Length of ICU and/or CCU stay for index AHF hosp. |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6545 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2103 |
| Method | Wilcoxon rank sum test |

Secondary: Percentage of participants with first improvement since baseline in

congestive signs and symptoms of heart failure

| | |
|-----------------|--|
| End point title | Percentage of participants with first improvement since baseline in congestive signs and symptoms of heart failure |
|-----------------|--|

End point description:

The percentage of participants with first improvement since baseline in congestive signs and symptoms of heart failure was assessed. The signs and symptoms included exertional dyspnea, orthopnea, rales, jugular venous pressure and peripheral edema/pre-sacral edema.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Day 5 | |

| End point values | Serelaxin (RLX030) | Placebo | | |
|---|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3044 | 3039 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Exertional dyspnea (n=3044,3039) | 94.1 | 92.6 | | |
| Orthopnea (n=2937,2967) | 92.9 | 91.2 | | |
| Rales (n=2888,2877) | 94.1 | 93.7 | | |
| Jugular venous pressure (n=2054,2034) | 90.4 | 88.0 | | |
| Peripheral/pre-sacral edema (n=2597,2622) | 91.6 | 90.7 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | First improvement in exertional dyspnea |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6083 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.14 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | First improvement in orthopnea |
| Comparison groups | Serelaxin (RLX030) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 6083 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0051 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.14 |

Notes:

[5] - 2-sided p-value

| | |
|---|------------------------------|
| Statistical analysis title | First improvement in rales |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6083 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9962 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.05 |

Notes:

[6] - 2-sided p-value

| | |
|---|--|
| Statistical analysis title | First improvement in jugular venous pressure |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6083 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0196 ^[7] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 1.15 |

Notes:

[7] - 2-sided p-value

| | |
|-----------------------------------|--|
| Statistical analysis title | First improvement in peripheral/pre-sacral edema |
|-----------------------------------|--|

| | |
|---|------------------------------|
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 6083 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2158 ^[8] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.1 |

Notes:

[8] - 2-sided p-value

Secondary: Change from baseline in hsTroponin T biomarker

| | |
|------------------------|--|
| End point title | Change from baseline in hsTroponin T biomarker |
| End point description: | Blood samples were collected to assess the change from baseline in hsTroponin T. The geometric least square mean (LSM) of the ratio of the post-baseline value to the baseline value is presented. |
| End point type | Secondary |
| End point timeframe: | Baseline, Day 2, Day 5 and Day 14 |

| End point values | Serelaxin (RLX030) | Placebo | | |
|--|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 521 | 510 | | |
| Units: ug/L | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Day 2 (n=464,459) | 0.9808 (0.9452 to 1.0177) | 1.0432 (1.0052 to 1.0827) | | |
| Day 5 (n=458,449) | 0.9589 (0.9116 to 1.0087) | 1.0678 (1.0148 to 1.1237) | | |
| Day 14 (n=436,418) | 0.7813 (0.7374 to 0.8278) | 0.8611 (0.8119 to 0.9132) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Change from baseline in hsTroponin T biomarker |
| Statistical analysis description: | Day 2 |
| Comparison groups | Serelaxin (RLX030) v Placebo |

| | |
|---|------------------------|
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0209 |
| Method | Repeated measure model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8921 |
| upper limit | 0.9907 |

| | |
|---|--|
| Statistical analysis title | Change from baseline in hsTroponin T biomarker |
| Statistical analysis description: | |
| Day 5 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0034 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8358 |
| upper limit | 0.9649 |

| | |
|---|--|
| Statistical analysis title | Change from baseline in hsTroponin T biomarker |
| Statistical analysis description: | |
| Day 14 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0209 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8355 |
| upper limit | 0.9854 |

| | |
|---|---|
| Secondary: Change from baseline in NT-proBNP biomarker | |
| End point title | Change from baseline in NT-proBNP biomarker |

End point description:

Blood samples were collected to assess the change from baseline in NT-proBNP. The ratio of the post-baseline value to the baseline value is presented.

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

End point timeframe:

Baseline, Day 2, Day 5 and Day 14

| End point values | Serelaxin (RLX030) | Placebo | | |
|--|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 521 | 510 | | |
| Units: pg/mL | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Day 2 (n=472,465) | 0.4902 (0.4609 to 0.5214) | 0.5702 (0.5358 to 0.6068) | | |
| Day 5 (n=465,455) | 0.4249 (0.3950 to 0.4570) | 0.4454 (0.4138 to 0.4794) | | |
| Day 14 (n=446,429) | 0.4265 (0.3957 to 0.4596) | 0.4469 (0.4143 to 0.4822) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in NT-proBNP biomarker |
|-----------------------------------|---|

Statistical analysis description:

Day 2

| | |
|---|------------------------------|
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0007 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7876 |
| upper limit | 0.9385 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in NT-proBNP biomarker |
|-----------------------------------|---|

Statistical analysis description:

Day 5

| | |
|-------------------|------------------------------|
| Comparison groups | Serelaxin (RLX030) v Placebo |
|-------------------|------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3709 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.0579 |

| | |
|---|---|
| Statistical analysis title | Change from baseline in NT-proBNP biomarker |
| Statistical analysis description: | |
| Day 14 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3893 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8578 |
| upper limit | 1.0617 |

| | |
|---|--|
| Secondary: Change from baseline in Cystatin C biomarker | |
| End point title | Change from baseline in Cystatin C biomarker |
| End point description: | |
| Blood samples were collected to assess the change from baseline in Cystatin C. The ratio of the post-baseline value to the baseline value is presented. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 2, Day 5 and Day 14 | |

| End point values | Serelaxin (RLX030) | Placebo | | |
|--|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 521 | 510 | | |
| Units: mg/L | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Day 2 (n=474,465) | 1.0261 (1.0119 to 1.0406) | 1.0648 (1.0499 to 1.0799) | | |

| | | | | |
|--------------------|---------------------------|---------------------------|--|--|
| Day 5 (n=467,456) | 1.1171 (1.0976 to 1.1369) | 1.1259 (1.1061 to 1.1461) | | |
| Day 14 (n=445,432) | 1.1186 (1.0949 to 1.1429) | 1.1342 (1.1098 to 1.1591) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change from baseline in Cystatin C biomarker |
| Statistical analysis description: | |
| Day 2 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0003 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9447 |
| upper limit | 0.983 |

| | |
|---|--|
| Statistical analysis title | Change from baseline in Cystatin C biomarker |
| Statistical analysis description: | |
| Day 5 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5361 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9677 |
| upper limit | 1.0172 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Change from baseline in Cystatin C biomarker |
| Statistical analysis description: | |
| Day 14 | |
| Comparison groups | Serelaxin (RLX030) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1031 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.375 |
| Method | Repeated measures model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9567 |
| upper limit | 1.0169 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

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

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | RLX030 30 ug/kg/day |
|-----------------------|---------------------|

Reporting group description:

RLX030 30 ug/kg/day

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

Reporting group description:

Placebo

| Serious adverse events | RLX030 30 ug/kg/day | Placebo | |
|---|---------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 412 / 3257 (12.65%) | 424 / 3248 (13.05%) | |
| number of deaths (all causes) | 363 | 386 | |
| number of deaths resulting from adverse events | 6 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon neoplasm | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Lung adenocarcinoma metastatic | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mesothelioma | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinum neoplasm | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to liver | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic gastric cancer | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Waldenstrom's macroglobulinaemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Small cell lung cancer | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm rupture | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Arterial stenosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 14 / 3257 (0.43%) | 9 / 3248 (0.28%) | |
| occurrences causally related to treatment / all | 5 / 14 | 3 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Iliac artery embolism | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Subclavian steal syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Cardioversion | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toe amputation | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery bypass | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Cardiac death | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |

| | | | |
|---|------------------|------------------|--|
| Asthenia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extravasation | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug effect increased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion site phlebitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 4 / 3257 (0.12%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Non-cardiac chest pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent occlusion | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 6 / 3248 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 6 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Acquired phimosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 5 / 3248 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 7 / 3248 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 3257 (0.18%) | 5 / 3248 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercapnia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary cavitation | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 7 / 3248 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 1 / 5 | 0 / 2 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory depression | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 7 / 3257 (0.21%) | 10 / 3248 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 4 | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium tremens | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |

| | | | |
|---|------------------|------------------|--|
| Device battery issue | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device leakage | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure decreased | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|------------------|------------------|--|
| Cardiac output decreased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular resistance pulmonary increased | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Aortic restenosis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac valve replacement complication | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural myocardial infarction | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lumbar vertebral fracture | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural hypotension | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute left ventricular failure | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 7 / 3248 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 14 / 3257 (0.43%) | 12 / 3248 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 14 | 1 / 12 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 4 / 3257 (0.12%) | 9 / 3248 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 10 / 3257 (0.31%) | 13 / 3248 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 10 | 1 / 13 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular dissociation | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradyarrhythmia | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 4 / 3257 (0.12%) | 4 / 3248 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 3257 (0.12%) | 9 / 3248 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 7 | |
| Cardiac failure | | | |
| subjects affected / exposed | 62 / 3257 (1.90%) | 68 / 3248 (2.09%) | |
| occurrences causally related to treatment / all | 5 / 62 | 2 / 69 | |
| deaths causally related to treatment / all | 2 / 20 | 0 / 22 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 14 / 3257 (0.43%) | 8 / 3248 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 12 / 3257 (0.37%) | 9 / 3248 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 12 | 0 / 9 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Cardiogenic shock | | | |

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|---|-------------------|-------------------|--|
| subjects affected / exposed | 5 / 3257 (0.15%) | 6 / 3248 (0.18%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 6 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiorenal syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chordae tendinae rupture | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 17 / 3257 (0.52%) | 12 / 3248 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 18 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery perforation | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Defect conduction intraventricular | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 5 / 3248 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve stenosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 4 / 3248 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Sinus node dysfunction | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 4 / 3257 (0.12%) | 6 / 3248 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 5 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 14 / 3257 (0.43%) | 11 / 3248 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 14 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem stroke | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid sinus syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral artery embolism | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic stroke | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Epilepsy | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercapnic coma | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 11 / 3257 (0.34%) | 16 / 3248 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 6 | |
| Muscle contractions involuntary | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiculopathy | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 5 / 3257 (0.15%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 6 / 3257 (0.18%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular encephalopathy | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 3257 (0.21%) | 7 / 3248 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia macrocytic | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heparin-induced thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Diarrhoea | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematochezia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal stenosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Alcoholic liver disease | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic congestion | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panniculitis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 20 / 3257 (0.61%) | 25 / 3248 (0.77%) | |
| occurrences causally related to treatment / all | 4 / 20 | 3 / 28 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 5 | |
| Anuria | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 4 / 3257 (0.12%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy toxic | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 6 / 3248 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 13 / 3257 (0.40%) | 9 / 3248 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 13 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Renal failure | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 10 / 3257 (0.31%) | 16 / 3248 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 10 | 2 / 16 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal mass | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Facial asymmetry | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspergilloma | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 9 / 3257 (0.28%) | 4 / 3248 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic hepatitis B | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis bacterial | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis bacterial | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nosocomial infection | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 34 / 3257 (1.04%) | 32 / 3248 (0.99%) | |
| occurrences causally related to treatment / all | 1 / 34 | 0 / 32 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 4 | |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 6 / 3257 (0.18%) | 8 / 3248 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Septic shock | | | |
| subjects affected / exposed | 4 / 3257 (0.12%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 2 / 3257 (0.06%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection pseudomonal | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 3257 (0.40%) | 5 / 3248 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 3 / 3248 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 3257 (0.09%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 2 / 3248 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 3257 (0.03%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 3257 (0.03%) | 0 / 3248 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic alkalosis | | | |
| subjects affected / exposed | 0 / 3257 (0.00%) | 1 / 3248 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0.5 %

| Non-serious adverse events | RLX030 30 ug/kg/day | Placebo | |
|---|--------------------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1336 / 3257 (41.02%) | 1277 / 3248 (39.32%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 23 / 3257 (0.71%) | 37 / 3248 (1.14%) | |
| occurrences (all) | 24 | 37 | |
| Hypotension | | | |
| subjects affected / exposed | 69 / 3257 (2.12%) | 58 / 3248 (1.79%) | |
| occurrences (all) | 69 | 58 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 31 / 3257 (0.95%) | 41 / 3248 (1.26%) | |
| occurrences (all) | 31 | 41 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 12 / 3257 (0.37%) | 20 / 3248 (0.62%) | |
| occurrences (all) | 13 | 20 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 6 / 3257 (0.18%) | 17 / 3248 (0.52%) | |
| occurrences (all) | 8 | 17 | |
| Epistaxis | | | |
| subjects affected / exposed | 19 / 3257 (0.58%) | 14 / 3248 (0.43%) | |
| occurrences (all) | 19 | 14 | |
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 3257 (0.52%) | 15 / 3248 (0.46%) | |
| occurrences (all) | 17 | 15 | |
| Cough | | | |
| subjects affected / exposed | 41 / 3257 (1.26%) | 36 / 3248 (1.11%) | |
| occurrences (all) | 41 | 36 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 16 / 3257 (0.49%) | 30 / 3248 (0.92%) | |
| occurrences (all) | 17 | 31 | |
| Insomnia | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 42 / 3257 (1.29%) 42 | 48 / 3248 (1.48%) 48 | |
| Confusional state subjects affected / exposed occurrences (all) | 25 / 3257 (0.77%) 25 | 28 / 3248 (0.86%) 28 | |
| Investigations | | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 36 / 3257 (1.11%) 36 | 49 / 3248 (1.51%) 49 | |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 15 / 3257 (0.46%) 15 | 20 / 3248 (0.62%) 21 | |
| Blood pressure decreased subjects affected / exposed occurrences (all) | 36 / 3257 (1.11%) 37 | 23 / 3248 (0.71%) 23 | |
| Blood urea increased subjects affected / exposed occurrences (all) | 24 / 3257 (0.74%) 24 | 25 / 3248 (0.77%) 25 | |
| Blood pressure systolic decreased subjects affected / exposed occurrences (all) | 29 / 3257 (0.89%) 29 | 24 / 3248 (0.74%) 24 | |
| Cardiac disorders | | | |
| Angina pectoris subjects affected / exposed occurrences (all) | 17 / 3257 (0.52%) 17 | 15 / 3248 (0.46%) 15 | |
| Aortic valve stenosis subjects affected / exposed occurrences (all) | 23 / 3257 (0.71%) 23 | 13 / 3248 (0.40%) 13 | |
| Aortic valve incompetence subjects affected / exposed occurrences (all) | 21 / 3257 (0.64%) 21 | 25 / 3248 (0.77%) 25 | |
| Cardiac failure subjects affected / exposed occurrences (all) | 162 / 3257 (4.97%) 164 | 185 / 3248 (5.70%) 191 | |
| Bradycardia | | | |

| | | | |
|--------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 23 / 3257 (0.71%) | 22 / 3248 (0.68%) | |
| occurrences (all) | 23 | 22 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 46 / 3257 (1.41%) | 45 / 3248 (1.39%) | |
| occurrences (all) | 47 | 47 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 52 / 3257 (1.60%) | 47 / 3248 (1.45%) | |
| occurrences (all) | 52 | 47 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 37 / 3257 (1.14%) | 24 / 3248 (0.74%) | |
| occurrences (all) | 38 | 25 | |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 30 / 3257 (0.92%) | 21 / 3248 (0.65%) | |
| occurrences (all) | 30 | 21 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 27 / 3257 (0.83%) | 17 / 3248 (0.52%) | |
| occurrences (all) | 27 | 17 | |
| Headache | | | |
| subjects affected / exposed | 74 / 3257 (2.27%) | 92 / 3248 (2.83%) | |
| occurrences (all) | 76 | 95 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 48 / 3257 (1.47%) | 47 / 3248 (1.45%) | |
| occurrences (all) | 48 | 47 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 3257 (0.55%) | 19 / 3248 (0.58%) | |
| occurrences (all) | 18 | 19 | |
| Constipation | | | |
| subjects affected / exposed | 70 / 3257 (2.15%) | 57 / 3248 (1.75%) | |
| occurrences (all) | 70 | 57 | |
| Diarrhoea | | | |
| subjects affected / exposed | 44 / 3257 (1.35%) | 52 / 3248 (1.60%) | |
| occurrences (all) | 44 | 52 | |
| Nausea | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 59 / 3257 (1.81%) | 51 / 3248 (1.57%) | |
| occurrences (all) | 59 | 51 | |
| Vomiting | | | |
| subjects affected / exposed | 30 / 3257 (0.92%) | 24 / 3248 (0.74%) | |
| occurrences (all) | 31 | 24 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 20 / 3257 (0.61%) | 20 / 3248 (0.62%) | |
| occurrences (all) | 20 | 20 | |
| Renal failure | | | |
| subjects affected / exposed | 42 / 3257 (1.29%) | 46 / 3248 (1.42%) | |
| occurrences (all) | 42 | 46 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 35 / 3257 (1.07%) | 34 / 3248 (1.05%) | |
| occurrences (all) | 35 | 34 | |
| Renal impairment | | | |
| subjects affected / exposed | 48 / 3257 (1.47%) | 55 / 3248 (1.69%) | |
| occurrences (all) | 49 | 55 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 22 / 3257 (0.68%) | 26 / 3248 (0.80%) | |
| occurrences (all) | 22 | 26 | |
| Muscle spasms | | | |
| subjects affected / exposed | 79 / 3257 (2.43%) | 49 / 3248 (1.51%) | |
| occurrences (all) | 82 | 50 | |
| Arthralgia | | | |
| subjects affected / exposed | 25 / 3257 (0.77%) | 21 / 3248 (0.65%) | |
| occurrences (all) | 25 | 22 | |
| Pain in extremity | | | |
| subjects affected / exposed | 27 / 3257 (0.83%) | 32 / 3248 (0.99%) | |
| occurrences (all) | 27 | 33 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 3257 (0.52%) | 22 / 3248 (0.68%) | |
| occurrences (all) | 17 | 22 | |
| Cystitis | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 18 / 3257 (0.55%) 18 | 7 / 3248 (0.22%) 7 | |
| Bronchitis subjects affected / exposed occurrences (all) | 30 / 3257 (0.92%) 30 | 47 / 3248 (1.45%) 47 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 58 / 3257 (1.78%) 58 | 68 / 3248 (2.09%) 68 | |
| Metabolism and nutrition disorders | | | |
| Gout subjects affected / exposed occurrences (all) | 16 / 3257 (0.49%) 16 | 28 / 3248 (0.86%) 28 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 40 / 3257 (1.23%) 40 | 36 / 3248 (1.11%) 36 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 25 / 3257 (0.77%) 25 | 17 / 3248 (0.52%) 17 | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 25 / 3257 (0.77%) 25 | 21 / 3248 (0.65%) 21 | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 29 / 3257 (0.89%) 29 | 22 / 3248 (0.68%) 24 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 263 / 3257 (8.07%) 268 | 241 / 3248 (7.42%) 250 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 19 / 3257 (0.58%) 19 | 13 / 3248 (0.40%) 13 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 22 August 2013 | <p>Amendment 1 introduced the following changes in order to comply with Health Authority requests stemming from the Volunteer Harmonization Procedure:</p> <ul style="list-style-type: none">• A criterion was added excluding patients with hematocrit < 25%, or a history of blood transfusion within the 14 days prior to Screening, or active life-threatening gastrointestinal bleeding.• ECG assessments were included at Screening and at Day 5 or Discharge, whichever occurred first.• An echocardiogram was included. The echocardiogram had to be performed during the index hospitalization, to determine a patient's ejection fraction which was used to classify the type of HF for subgroup analysis. The echocardiogram was to be performed as soon as possible post randomization, and prior to Discharge.• The follow up period was changed from a minimum of 14 days to 180 days for the case the study was concluded early for efficacy following the interim analysis.• A minor clarification was made to the timing of the ECG sub-study: the first sub-study ECG was to be performed at Baseline, not at Screening.• A minor clarification was made to the Laboratory sub-study urine assessment: the data was to be maintained in the source documents only and not in the database. |
| 23 September 2013 | <p>Amendment 2 introduced the following changes:</p> <ul style="list-style-type: none">• In the original protocol, all-cause death through Day 180 was not included in the multiple testing procedure of the key secondary efficacy variables, i.e., only the other 3 key secondary efficacy variables were included. As per feedback from FDA, all 4 key secondary efficacy variables were included in the multiple testing procedure, so the overall type I error including all-cause death and other 3 key efficacy variables was controlled at 5% alpha level.• In addition, a minor change was made to the Physician assessment of signs and symptoms criteria. NA, not evaluable, was removed from the assessments for exertional dyspnea and orthopnea. This was done to avoid confusion during data collection between when the evaluation was not evaluable (patient was immobile) and when the evaluation was simply not done. |
| 06 January 2014 | <p>Amendment 3 introduced the following changes:</p> <ul style="list-style-type: none">• Exclusion criterion #8 was amended criteria to exclude current treatment within 2 hours prior to randomization (and not at Screening) in order to improve patient recruitment.• Additional information about 5% dextrose infusion bags and materials which can be used during preparation of study treatment was included.• Filter name was updated based on the availability of a new brand name.• The timing of the physical examination was clarified due to inconsistency with the assessment schedule.• The summary of Amendment 2 was updated to remove the requirement for IRB/EC protocol approval prior to implementation since this was not valid in select countries.• Schedule of assessments table was updated to clarify the intervals for collection of WHF assessment (at hours 24, 48, 72, 96 and 120) as part of the physician assessment of HF signs and symptoms.• The safety set definition was updated to clarify a statement that any patient who has received serelaxin was included as part of the serelaxin treatment group.• Time-to-event was changed to be defined as randomization to the event.• Length of stay definition was changed to index hospitalization discharge date and time minus the randomization date and time. |

| | |
|-------------------|---|
| 09 September 2014 | <p>Amendment 4 introduced the changes to improve the overall clarity of the study inclusion and exclusion criteria: Some of the changes included: Inclusion criteria:</p> <ul style="list-style-type: none"> • The criteria for hospitalization due to AHF were enhanced to read: hospitalized for AHF with the anticipated requirement of i.v. therapy (including i.v. diuretics) for at least 48 hours. • The dyspnea at rest criteria was enhanced to read: persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for AHF including the protocol required i.v. furosemide of at least 40 mg total (or equivalent). • The BNP and NT proBNP criteria were increased to $\text{BNP} \geq 500 \text{ pg/mL}$ or $\text{NT-proBNP} \geq 2,000 \text{ pg/mL}$. The following BNP and NT proBNP criteria were also added: for patients ≥ 75 years of age or with current atrial fibrillation (at the time of randomization), $\text{BNP} \geq 750 \text{ pg/mL}$ or $\text{NT-proBNP} \geq 3,000 \text{ pg/mL}$. • The inclusion criteria for i.v. furosemide were updated to add the following criteria: Time from presentation to start of furosemide administration was to be less than 6 hours. |
| 18 February 2015 | <p>Amendment 5 introduced the following changes:</p> <ul style="list-style-type: none"> • The reduction of WHF events through Day 5 was added as an additional primary endpoint. • The target number of CV deaths and the sample size was increased to adjust for the alpha-split required to accommodate the additional primary objective. • Minor changes to provide some clarity and flexibility around the conduct and timing of the study visits and visit procedures. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported