# Clinical trial results:
# A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF)

## Summary

| | |
|---|---|
| EudraCT number | 2016-002280-34 |
| Trial protocol | DE NL FR ES HU CZ BE GB IT |
| Global end of trial date | 28 May 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 12 June 2021 |
| First version publication date | 12 June 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 1245.121 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03057977 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Straße 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 14 July 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this event-driven trial was to demonstrate superiority of empagliflozin 10 mg versus placebo on top of guideline-directed medical therapy in patients with symptomatic, chronic HF and reduced left ventricular ejection fraction (LVEF ≤40%).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 06 April 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 911 |
| Country: Number of subjects enrolled | Australia: 56 |
| Country: Number of subjects enrolled | Belgium: 78 |
| Country: Number of subjects enrolled | Brazil: 1629 |
| Country: Number of subjects enrolled | Canada: 344 |
| Country: Number of subjects enrolled | China: 278 |
| Country: Number of subjects enrolled | Czechia: 194 |
| Country: Number of subjects enrolled | Germany: 231 |
| Country: Number of subjects enrolled | Spain: 73 |
| Country: Number of subjects enrolled | France: 95 |
| Country: Number of subjects enrolled | United Kingdom: 100 |
| Country: Number of subjects enrolled | Hungary: 200 |
| Country: Number of subjects enrolled | India: 261 |
| Country: Number of subjects enrolled | Italy: 176 |
| Country: Number of subjects enrolled | Japan: 343 |
| Country: Number of subjects enrolled | Korea, Republic of: 150 |
| Country: Number of subjects enrolled | Mexico: 184 |
| Country: Number of subjects enrolled | Netherlands: 338 |
| Country: Number of subjects enrolled | Poland: 874 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 705 |
| Worldwide total number of subjects | 7220 |
| EEA total number of subjects | 2259 |

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) | 3144 |
| From 65 to 84 years | 3909 |
| 85 years and over | 167 |

## Subject disposition

### Recruitment

Recruitment details:

A randomised, double-blind trial to demonstrate superiority of empagliflozin versus placebo, in patients with chronic Heart Failure with reduced Ejection Fraction (HFrEF).

### Pre-assignment

Screening details:

Patients were included in the trial after they had signed the informed consent form (ICF). All patients who met the all inclusion and none of the exclusion criteria during screening and at the randomisation approximately 1 to 4 weeks later were randomised to empagliflozin or placebo in a 1:1 ratio.

### Period 1

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

Blinding implementation details:

Patients, investigators and everyone involved in the trial conduct or analysis or with any other interest in this double-blind trial remaind blinded with regard to the randomised treatment assignements until after database lock.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

1 film-coated tablet of matching placebo was administered orally once daily.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 film-coated tablet of matching placebo was administered orally once daily.

| | |
|---|---|
| **Arm title** | 10 mg Empagliflozin |

Arm description:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Empagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

| **Number of subjects in period 1[1]** | Placebo | 10 mg Empagliflozin |
|---|---|---|
| Started | 1867 | 1863 |
| Treated | 1863 | 1863 |
| Completed | 1352 | 1381 |
| Not completed | 515 | 482 |
| Adverse Event | 343 | 337 |
| Principle Investigator Decision | 2 | - |
| Patient decision to stop/interrupt medication | 8 | 6 |
| Personal Reasons | 1 | 1 |
| Other medical condition (no Adverse Event) | 2 | 4 |
| Unblinded medication | 1 | - |
| Not treated | 4 | - |
| Consent withdrawn by subject | 124 | 92 |
| Unable to continue treatment | 4 | 1 |
| Reason Unknown | - | 1 |
| Patient received Empagliflozin for Diabetes | 1 | 1 |
| Lost to follow-up | 11 | 17 |
| Patient moved away/being abroad | 4 | 3 |
| Not attending study visit | 3 | 10 |
| Due to Covid-19 Pandemic | 1 | 4 |
| Protocol deviation | 6 | 5 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 7220 patient were enrolled world wide, whereas 3730 patients actually started the trial.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| 1 film-coated tablet of matching placebo was administered orally once daily. | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: | |
| Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily. | |

| Reporting group values | Placebo | 10 mg Empagliflozin | Total |
|---|---|---|---|
| Number of subjects | 1867 | 1863 | 3730 |
| Age categorical | | | |
| Randomised Set (RS): All randomised patients. | | | |
| 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) | 740 | 675 | 1415 |
| From 65-84 years | 1086 | 1130 | 2216 |
| 85 years and over | 41 | 58 | 99 |
| Age Continuous | | | |
| Randomised Set (RS): All randomised patients. | | | |
| Units: years | | | |
| arithmetic mean | 66.5 | 67.2 | |
| standard deviation | ± 11.2 | ± 10.8 | - |
| Sex: Female, Male | | | |
| Randomised Set (RS): All randomised patients. | | | |
| Units: Subjects | | | |
| Female | 456 | 437 | 893 |
| Male | 1411 | 1426 | 2837 |
| Race (NIH/OMB) | | | |
| Randomised Set (RS): All randomised patients. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 24 | 15 | 39 |
| Asian | 335 | 337 | 672 |
| Native Hawaiian or Other Pacific Islander | 6 | 8 | 14 |
| Black or African American | 134 | 123 | 257 |
| White | 1304 | 1325 | 2629 |
| More than one race | 33 | 28 | 61 |
| Unknown or Not Reported | 31 | 27 | 58 |
| Ethnicity (NIH/OMB) | | | |
| Randomised Set (RS): All randomised patients. | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Hispanic or Latino | 613 | 616 | 1229 |
| Not Hispanic or Latino | 1178 | 1164 | 2342 |
| Unknown or Not Reported | 76 | 83 | 159 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| 1 film-coated tablet of matching placebo was administered orally once daily. | |
| Reporting group title | 10 mg Empagliflozin |
| Reporting group description: | |
| Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily. | |

### Primary: Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF)

| | |
|---|---|
| End point title | Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF) |
| End point description: | |
| Time to the first event of adjudicated cardiovascular (CV) death or adjudicated hospitalisation for heart failure (HHF). The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk. | |
| End point type | Primary |
| End point timeframe: | |
| From randomisation until completion of the planned treatment period, up to 1040 days. | |

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[1] | 1863[2] | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 21.00 (19.13 to 22.96) | 15.77 (14.19 to 17.44) | | |

Notes:

[1] - RS

[2] - RS

### Statistical analyses

| Statistical analysis title | Cox regression model |
|---|---|
| Statistical analysis description: | |
| Model with terms for age, baseline eGFR (CKD-EPK)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. alpha = 0.0496 (resulting from interim analysis) eGFR (CKP-EPI)cr: Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement LVEF: Left ventricular ejection fraction. | |
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95.04 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.86 |

## Secondary: Occurrence of adjudicated Hospitalisation for Heart Failure (HHF) (first and recurrent)

| | |
|---|---|
| End point title | Occurrence of adjudicated Hospitalisation for Heart Failure (HHF) (first and recurrent) |

End point description:

Reported is the total number of HHF events (first and recurrent) which occurred. All data up to the end of the planned treatment period (including the data after the end of treatment for patients not completing the treatment period as planned) from all randomised patients was used. Randomised Set (RS): All randomised patients.

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

End point timeframe:

From randomisation until completion of the planned treatment phase, up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[3] | 1863[4] | | |
| Units: HHF events | 553 | 388 | | |

Notes:

[3] - RS

[4] - RS

### Statistical analyses

| **Statistical analysis title** | Joint frailty model |
|---|---|

Statistical analysis description:

Model accounts for dependence between recurrent HHF and cardiovascular death, with terms for age, baseline eGFR (CKD-EPK)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. eGFR (CKP-EPI)cr: Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement LVEF: Left ventricular ejection fraction.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0003 |
| Method | Joint frailty model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95.04 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.85 |

## Secondary: eGFR (CKD-EPI) cr slope of change from baseline

| | |
|---|---|
| End point title | eGFR (CKD-EPI) cr slope of change from baseline |

End point description:

Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (eGFR (CKD-EPI)cr) [mL/min/1.73m2] slope of change from baseline. Available on-treatment change-from-baseline data were to be used. Patients without on-treatment data after randomisation were not to be included in this analysis. Slope represents the long term effect on eGFR. Timepoints after baseline were included in calculation of slope of change from baseline. Descriptive statistic (mean(standard error)) is reported. Treated Set (TS): All patients treated with at least one dose of the study medication and at least one on-treatment measurement of eGFR.

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

End point timeframe:

Assessed at baseline, week 4, 12, 32, 52, 76, 100, 124, 148 and at end of treatment (EOT), up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1792[5] | 1799[6] | | |
| Units: Milliliter/minute/1.73 meters squared | | | | |
| arithmetic mean (standard error) | -2.278 (± 0.229) | -0.546 (± 0.227) | | |

Notes:

[5] - TS

[6] - TS

### Statistical analyses

| **Statistical analysis title** | Random coefficient model |
|---|---|

Statistical analysis description:

Random coefficient model allowing for random intercept and random slope per patient, with the same factors used for the primary endpoint (age, baseline eGFR (CKD-EPK)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment) and additional factors “time”, “treatment-by-time interaction”, and “baseline eGFR (CKD-EPI)cr-by-time interaction”. Only “on-treatment” data from treated patients were used. alpha=0.001

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |

| | |
|---|---|
| Number of subjects included in analysis | 3591 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Random intercept random coef. model |
| Parameter estimate | Treatment by time interaction |
| Point estimate | 1.733 |
| Confidence interval | |
| level | Other: 99.9 % |
| sides | 2-sided |
| lower limit | 0.669 |
| upper limit | 2.796 |

## Secondary: Time to first event in composite renal endpoint: chronic dialysis, renal transplant or sustained reduction of eGFR(CKD-EPI)cr

| | |
|---|---|
| End point title | Time to first event in composite renal endpoint: chronic dialysis, renal transplant or sustained reduction of eGFR(CKD-EPI)cr |

End point description:

Time to the first event in the composite renal endpoint: chronic dialysis (with a frequency of twice per week or more for at least 90 days), renal transplant, or sustained reduction in Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (eGFR (CKD-EPI)cr). The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

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

End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[7] | 1863[8] | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 3.07 (2.33 to 3.91) | 1.56 (1.06 to 2.17) | | |

Notes:

[7] - RS

[8] - RS

### Statistical analyses

| **Statistical analysis title** | Cox regression model |
|---|---|
| Comparison groups | 10 mg Empagliflozin v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0019 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 0.77 |

## Secondary: Time to first adjudicated Hospitalisation for Heart Failure (HHF)

| | |
|---|---|
| End point title | Time to first adjudicated Hospitalisation for Heart Failure (HHF) |

End point description:

Time to first adjudicated Hospitalisation for Heart Failure (HHF). The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

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

End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[9] | 1863[10] | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 15.55 (13.94 to 17.24) | 10.75 (9.45 to 12.13) | | |

Notes:

[9] - RS

[10] - RS

### Statistical analyses

| **Statistical analysis title** | Cox regression model |
|---|---|
| Comparison groups | 10 mg Empagliflozin v Placebo |
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.81 |

## Secondary: Time to adjudicated cardiovascular (CV) death

| | |
|---|---|
| End point title | Time to adjudicated cardiovascular (CV) death |

End point description:

Time to adjudicated CV (Cardiovascular) death. The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

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

End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[11] | 1863[12] | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 8.13 (7.05 to 9.29) | 7.55 (6.51 to 8.67) | | |

Notes:

[11] - RS

[12] - RS

### Statistical analyses

| Statistical analysis title | Cox regression model |
|---|---|
| Comparison groups | 10 mg Empagliflozin v Placebo |
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4133 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.12 |

## Secondary: Time to all-cause mortality

| End point title | Time to all-cause mortality |
|---|---|

End point description:

Time to all-cause mortality. The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Randomised Set (RS): All randomised patients. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

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

End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

| End point values | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[13] | 1863[14] | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 10.71 (9.46 to 12.04) | 10.06 (8.85 to 11.34) | | |

Notes:

[13] - RS

[14] - RS

### Statistical analyses

| Statistical analysis title | Cox regression model |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3536 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.1 |

## Secondary: Time to onset of Diabetis Mellitus (DM)

| End point title | Time to onset of Diabetis Mellitus (DM) |
|---|---|

End point description:

Time to onset of DM (Glycated haemoglobin (HbA1c) ≥6.5% or as diagnosed by the investigator) in patients with pre-DM (no history of DM and no HbA1c ≥6.5% before treatment, and a pre-treatment HbA1c value of 5.7 to <6.5%). The incidence rate (patients with events per 100 person years at risk) is reported. The incidence rate per 100 patient years (100 * number of patients with event /time at risk [years]) is presented. With time at risk [year] calculated as: Sum of time at risk [days] over all patients in a treatment group / 365.25. Patients without a specific endpoint event were censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Patients in the randomised set with pre-DM. Unit of Measure: Patients with events per 100 patient-years (pt-yrs) at risk.

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

End point timeframe:

From randomisation until completion of the planned treatment period, up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 636 | 632 | | |
| Units: Patients with events/ 100 pt-yrs at risk | | | | |
| number (confidence interval 95%) | 10.62 (8.42 to 13.07) | 9.31 (7.27 to 11.60) | | |

**Statistical analyses**

| **Statistical analysis title** | Cox regression model |
|---|---|
| Comparison groups | 10 mg Empagliflozin v Placebo |
| Number of subjects included in analysis | 1268 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3576 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.19 |

## Secondary: Change from baseline in KCCQ (Kansas City cardiomyopathy questionnaire) clinical summary score at Week 52

| End point title | Change from baseline in KCCQ (Kansas City cardiomyopathy questionnaire) clinical summary score at Week 52 |
|---|---|

End point description:

The KCCQ is a 23-item self-administered questionnaire designed to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self efficacy, and quality of life in patients with Heart Failure. The KCCQ-clinical summary score comprises the following domains:

Symptom frequency, symptom burden and physical limitation. The score is calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. For patients who died, a worst score (score of 0) is imputed at all subsequent scheduled visits after the date of death. Standard error is adjusted standard error. Change from baseline in KCCQ-score at week 52 was modeled using a MMRM with visit (week 12, 32 and 52) as repeated measures, adjusted mean (standard error) at week 52 is reported. Patients in the randomized set (RS) with available data for this endpoint, including values obtained on treatment or post-treatment.

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

End point timeframe:

Assessed at baseline, week 12, week 32 and week 52.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1395 | 1401 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -3.36 (± 0.69) | -1.30 (± 0.69) | | |

**Statistical analyses**

| **Statistical analysis title** | Mixed model |
|---|---|

Statistical analysis description:

Mixed model with age, baseline eGFR (CKD-EPI) as linear covariate(s) and region, baseline diabetes status, sex, baseline LVEF, week reachable, treatment by visit interaction, baseline KCCQ - Clinical Summary Score by Visit interaction as fixed effects. An unstructured covariance structure has been used.

| Comparison groups | Placebo v 10 mg Empagliflozin |
|---|---|
| Number of subjects included in analysis | 2796 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.034 |
| Method | Mixed Model |
| Parameter estimate | Difference of adjusted means |
| Point estimate | 2.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.16 |
| upper limit | 3.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.97 |

**Secondary: Number of all-cause hospitalizations (first and recurrent)**

| End point title | Number of all-cause hospitalizations (first and recurrent) |
|---|---|

End point description:

Number of all-cause hospitalizations (first and recurrent). Randomised Set (RS): All randomised patients.

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

End point timeframe:

From randomisation until completion of the planned treatment phase, up to 1040 days.

| **End point values** | Placebo | 10 mg Empagliflozin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1867[15] | 1863[16] | | |
| Units: Hospitalizations for any cause | 1570 | 1364 | | |

Notes:

[15] - RS

[16] - RS

### Statistical analyses

| **Statistical analysis title** | Joint frailty model |
|---|---|

Statistical analysis description:

Joint frailty model with terms for age, baseline eGFR (CDK-EPI), region, sex, baseline diabetes status and baseline LVEF. Model accounts for dependence between recurrent all-cause hospitalizations and all-cause mortality.

| | |
|---|---|
| Comparison groups | Placebo v 10 mg Empagliflozin |
| Number of subjects included in analysis | 3730 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0065 |
| Method | Joint frailty model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 0.95 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

[All-Cause Mortality]: From randomization until end of planned treatment period, up to 1040 days. [Serious/Other AE]: From first intake of study medication until end of planned treatment period + 7 days (Residual Effect Period), up to 1047 days.

Adverse event reporting additional description:

[All-Cause Mortality]: Randomised Set: All randomised patients. The actual number of participants at risk for all-cause deaths is 1867 for Placebo group. [Serious Adverse Events and Other Adverse Events]: Treated Set: All patients treated with at least one dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

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

Reporting group description:

1 film-coated tablet of matching placebo was administered orally once daily.

| | |
|---|---|
| Reporting group title | 10 mg Empagliflozin |

Reporting group description:

Film-coated tablet of 10 milligram (mg) Empagliflozin was administered orally once daily.

| Serious adverse events | Placebo | 10 mg Empagliflozin | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 896 / 1863 (48.09%) | 772 / 1863 (41.44%) | |
| number of deaths (all causes) | 266 | 249 | |
| number of deaths resulting from adverse events | 2 | 7 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Abdominal neoplasm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of the cervix | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma pancreas | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Adrenal adenoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct adenocarcinoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer stage IV | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myelomonocytic leukaemia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cutaneous T-cell lymphoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Diffuse large B-cell lymphoma recurrent | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal neoplasm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cancer | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypergammaglobulinaemia benign monoclonal | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic carcinoma of the bladder | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian adenoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 7 / 1863 (0.38%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer metastatic | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric cancer | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic intramural haematoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Deep vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 1863 (0.27%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery embolism | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive urgency | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 13 / 1863 (0.70%) | 14 / 1863 (0.75%) | |
| occurrences causally related to treatment / all | 2 / 14 | 4 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leriche syndrome | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocele | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 1 / 1863 (0.05%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 1863 (0.21%) | 7 / 1863 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery occlusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein occlusion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subgaleal haemorrhage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular insufficiency | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Surgical and medical procedures** | | | |
| Cardiac resynchronisation therapy | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardioversion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implantable defibrillator insertion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Percutaneous coronary intervention | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Cardiac death | | | |
| subjects affected / exposed | 8 / 1863 (0.43%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 8 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 8 | 2 / 4 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 27 / 1863 (1.45%) | 20 / 1863 (1.07%) | |
| occurrences causally related to treatment / all | 1 / 27 | 1 / 20 | |
| deaths causally related to treatment / all | 1 / 27 | 1 / 20 | |
| Discomfort | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Euthanasia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Foreign body reaction | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site haematoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site haematoma | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 7 / 1863 (0.38%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema due to cardiac disease | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stent-graft endoleak | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 10 / 1863 (0.54%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 8 | |
| deaths causally related to treatment / all | 1 / 10 | 0 / 8 | |
| Sudden death | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device occlusion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vessel puncture site phlebitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Immune system disorders** | | | |
| Heart transplant rejection | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Reproductive system and breast disorders** | | | |

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|---|---|---|---|
| Acquired hydrocele | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibrocystic breast disease | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterovaginal prolapse | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 2 / 1863 (0.11%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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|---|---|---|---|
| Asthma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 13 / 1863 (0.70%) | 11 / 1863 (0.59%) | |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 7 / 1863 (0.38%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paranasal cyst | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord thickening | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Psychiatric disorders** | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Delirium | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 1863 (0.21%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium tremens | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug abuse | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device failure | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device inappropriate shock delivery | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device lead damage | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device lead issue | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device physical property issue | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac cirrhosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 5 / 1863 (0.27%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-alcoholic steatohepatitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac electrophysiologic study | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endoscopic retrograde cholangiopancreatography | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme abnormal | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | | | |

| | | | |
|---|---|---|---|
| Ankle fracture | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Avulsion fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder injury | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carbon monoxide poisoning | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Costal cartilage fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 15 / 1863 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Heat stroke | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple injuries | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Open globe injury | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural swelling | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post-traumatic pain | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative respiratory failure | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural shock | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic rupture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Dermoid cyst | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal arteriovenous malformation | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phimosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type IV hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 7 / 1863 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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|---|---|---|---|
| Acute myocardial infarction | | | |
| subjects affected / exposed | 18 / 1863 (0.97%) | 24 / 1863 (1.29%) | |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 24 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 11 | |
| Angina pectoris | | | |
| subjects affected / exposed | 10 / 1863 (0.54%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 9 / 1863 (0.48%) | 11 / 1863 (0.59%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 44 / 1863 (2.36%) | 24 / 1863 (1.29%) | |
| occurrences causally related to treatment / all | 1 / 49 | 1 / 30 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 1863 (0.59%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac aneurysm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 10 / 1863 (0.54%) | 9 / 1863 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 9 | |
| Cardiac asthma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac dysfunction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 444 / 1863 (23.83%) | 332 / 1863 (17.82%) | |
| occurrences causally related to treatment / all | 9 / 687 | 7 / 494 | |
| deaths causally related to treatment / all | 0 / 39 | 1 / 41 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 29 / 1863 (1.56%) | 19 / 1863 (1.02%) | |
| occurrences causally related to treatment / all | 2 / 46 | 0 / 32 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 32 / 1863 (1.72%) | 18 / 1863 (0.97%) | |
| occurrences causally related to treatment / all | 1 / 53 | 1 / 33 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Cardiac failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 41 / 1863 (2.20%) | 26 / 1863 (1.40%) | |
| occurrences causally related to treatment / all | 3 / 62 | 1 / 38 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 11 / 1863 (0.59%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 1 / 11 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | |
| Cardiomegaly | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiorenal syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic left ventricular failure | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 6 / 1863 (0.32%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 16 / 1863 (0.86%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 16 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary ostial stenosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracardiac thrombus | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Low cardiac output syndrome | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 16 / 1863 (0.86%) | 16 / 1863 (0.86%) | |
| occurrences causally related to treatment / all | 0 / 17 | 1 / 17 | |
| deaths causally related to treatment / all | 0 / 7 | 1 / 8 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paroxysmal atrioventricular block | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prinzmetal angina | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 6 / 1863 (0.32%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torsade de pointes | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trifascicular block | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 5 / 1863 (0.27%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 8 / 1863 (0.43%) | 10 / 1863 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Ventricular flutter | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 37 / 1863 (1.99%) | 55 / 1863 (2.95%) | |
| occurrences causally related to treatment / all | 1 / 46 | 2 / 73 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid arteriosclerosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar stroke | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral hypoperfusion | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 12 / 1863 (0.64%) | 17 / 1863 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 13 | 2 / 17 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 4 | |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolic stroke | | | |

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| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Headache | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemic seizure | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 20 / 1863 (1.07%) | 19 / 1863 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 21 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 2 | |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoclonus | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postresuscitation encephalopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 0 / 1863 (0.00%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 8 / 1863 (0.43%) | 17 / 1863 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 9 / 1863 (0.48%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uraemic encephalopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular dementia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular encephalopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 6 / 1863 (0.32%) | 10 / 1863 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood loss anaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic haematoma | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic infarction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mixed deafness | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Eye disorders** | | | |
| Cataract | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract cortical | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glaucoma | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular degeneration | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Open angle glaucoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal tear | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coeliac disease | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erosive oesophagitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric mucosa erythema | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal vascular malformation haemorrhagic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 7 / 1863 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intussusception | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery stenosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontal disease | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngo-oesophageal diverticulum | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 7 / 1863 (0.38%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vomiting | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angioedema | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 | 3 / 1863 (0.16%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stasis dermatitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 55 / 1863 (2.95%) | 35 / 1863 (1.88%) | |
| occurrences causally related to treatment / all | 8 / 59 | 6 / 40 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Azotaemia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 6 / 1863 (0.32%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diabetic nephropathy | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| End stage renal disease | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nephropathy toxic | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 14 / 1863 (0.75%) | 9 / 1863 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 14 | 2 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Renal impairment | | | |
| subjects affected / exposed | 27 / 1863 (1.45%) | 17 / 1863 (0.91%) | |
| occurrences causally related to treatment / all | 5 / 27 | 2 / 17 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal infarct | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthropathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crystal arthropathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint destruction | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 7 / 1863 (0.38%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polymyalgia rheumatica | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal sepsis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 5 / 1863 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bullous erysipelas | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (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 | 3 / 1863 (0.16%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| 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 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis viral | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye abscess | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fournier's gangrene | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis viral | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 9 / 1863 (0.48%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic fever | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Human anaplasmosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site infection | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective spondylitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Labyrinthitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site infection | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nail infection | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nocardiosis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic abscess | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perineal abscess | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 62 / 1863 (3.33%) | 53 / 1863 (2.84%) | |
| occurrences causally related to treatment / all | 0 / 63 | 2 / 56 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 5 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia chlamydial | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia influenzal | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchitis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 8 / 1863 (0.43%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Septic encephalopathy | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 9 / 1863 (0.48%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 5 | |
| Sinobronchitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord abscess | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 10 / 1863 (0.54%) | 14 / 1863 (0.75%) | |
| occurrences causally related to treatment / all | 6 / 10 | 5 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vessel puncture site cellulitis | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral diarrhoea | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Decreased appetite | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 1863 (0.21%) | 8 / 1863 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 4 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic complication | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 7 / 1863 (0.38%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 9 / 1863 (0.48%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 2 / 9 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 5 / 1863 (0.27%) | 6 / 1863 (0.32%) | |
| occurrences causally related to treatment / all | 4 / 7 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 3 / 1863 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 1863 (0.11%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 1863 (0.05%) | 0 / 1863 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 1863 (0.00%) | 2 / 1863 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 3 / 1863 (0.16%) | 4 / 1863 (0.21%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 1863 (0.00%) | 1 / 1863 (0.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | 10 mg Empagliflozin | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 369 / 1863 (19.81%) | 328 / 1863 (17.61%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 109 / 1863 (5.85%) | 120 / 1863 (6.44%) | |
| occurrences (all) | 120 | 132 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 94 / 1863 (5.05%) | 89 / 1863 (4.78%) | |
| occurrences (all) | 109 | 125 | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 109 / 1863 (5.85%) | 99 / 1863 (5.31%) | |
| occurrences (all) | 124 | 117 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 115 / 1863 (6.17%) | 63 / 1863 (3.38%) | |
| occurrences (all) | 120 | 66 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 November 2017 | The screening period was extended by 7 days. It was also clarified that screening procedures could be performed over multiple days; Additional criteria for N-terminal pro-brain natriuretic peptide (NT-proBNP) were added for patients with documented HHF in inclusion criterion 5; Implantable cardioverter defibrillator (ICD) and Cardiac resynchronisation therapy (CRT) (and intention to implant thereof) were added to exclusion criterion 29; The exploratory secondary endpoint "first occurrence of sustained reduction of ≥40% Estimated glomerular filtration rate (eGFR)" was further specified; An Electrocardiogram (ECG) was to be performed at screening rather than the baseline visit; For laboratory analyses at screening, a haematology panel was added while urinalysis was removed; A national coordinator committee was set up to advise on the trial. An explanation was added to the protocol; The ketone monitoring strategy for patients with Type 1 diabetes mellitus (T1DM) was added; The guidance to sites on the consent process for patients with T1DM was added. |
| 18 July 2018 | No major changes to the protocol were introduced by this amendment. The changes involved logistical or administrative aspects only and did not require Independent ethics committee (IEC)/ Institutional review board (IRB) approval (unless required by local regulations). |
| 20 November 2019 | The use of any Sodium-dependent glucose co-transporter (SGLT)-2/1 inhibitors was allowed during the 30 day-period between the end-of-trial visit (EOT) and the follow-up visit occurring at study close-out; Changes to the planned analyses to be consistent with the changes introduced by the TSAP. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported