



## Clinical trial results:

**A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2015-000990-11   |
| Trial protocol           | DK SE GB AT CZ ES FI PT BE NL FR DE LT PL GR RO IE SK IT |
| Global end of trial date | 14 April 2020  |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 22 April 2021 |
| First version publication date | 22 April 2021 |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 16244 |
|-----------------------|-------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02540993 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 April 2020 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 14 April 2020 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate whether, in addition to standard of care, finerenone is superior to placebo in delaying the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR)  $\geq 40\%$  from baseline over at least 4 weeks, or renal death.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Standard of care: individual maximum tolerated labeled dose of either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) (but not both)

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 17 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Austria: 62        |
| Country: Number of subjects enrolled | Belgium: 54        |
| Country: Number of subjects enrolled | Bulgaria: 225      |
| Country: Number of subjects enrolled | Switzerland: 10    |
| Country: Number of subjects enrolled | Czechia: 99        |
| Country: Number of subjects enrolled | Germany: 88        |
| Country: Number of subjects enrolled | Denmark: 111       |
| Country: Number of subjects enrolled | Spain: 260         |
| Country: Number of subjects enrolled | Finland: 62        |
| Country: Number of subjects enrolled | France: 64         |
| Country: Number of subjects enrolled | United Kingdom: 67 |
| Country: Number of subjects enrolled | Greece: 48         |
| Country: Number of subjects enrolled | Hungary: 140       |
| Country: Number of subjects enrolled | Ireland: 5         |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Italy: 206              |
| Country: Number of subjects enrolled | Lithuania: 9            |
| Country: Number of subjects enrolled | Netherlands: 72         |
| Country: Number of subjects enrolled | Norway: 26              |
| Country: Number of subjects enrolled | Poland: 112             |
| Country: Number of subjects enrolled | Portugal: 130           |
| Country: Number of subjects enrolled | Romania: 59             |
| Country: Number of subjects enrolled | Russian Federation: 263 |
| Country: Number of subjects enrolled | Slovakia: 7             |
| Country: Number of subjects enrolled | Sweden: 34              |
| Country: Number of subjects enrolled | Turkey: 72              |
| Country: Number of subjects enrolled | Ukraine: 73             |
| Country: Number of subjects enrolled | Canada: 107             |
| Country: Number of subjects enrolled | Puerto Rico: 13         |
| Country: Number of subjects enrolled | United States: 824      |
| Country: Number of subjects enrolled | China: 372              |
| Country: Number of subjects enrolled | Hong Kong: 61           |
| Country: Number of subjects enrolled | Israel: 252             |
| Country: Number of subjects enrolled | Japan: 415              |
| Country: Number of subjects enrolled | Korea, Republic of: 138 |
| Country: Number of subjects enrolled | Malaysia: 77            |
| Country: Number of subjects enrolled | Philippines: 45         |
| Country: Number of subjects enrolled | Singapore: 19           |
| Country: Number of subjects enrolled | Thailand: 36            |
| Country: Number of subjects enrolled | Taiwan: 111             |
| Country: Number of subjects enrolled | Vietnam: 53             |
| Country: Number of subjects enrolled | Argentina: 84           |
| Country: Number of subjects enrolled | Brazil: 176             |
| Country: Number of subjects enrolled | Chile: 31               |
| Country: Number of subjects enrolled | Colombia: 182           |
| Country: Number of subjects enrolled | Mexico: 120             |
| Country: Number of subjects enrolled | Australia: 63           |
| Country: Number of subjects enrolled | New Zealand: 38         |
| Country: Number of subjects enrolled | South Africa: 99        |
| Worldwide total number of subjects   | 5674                    |
| EEA total number of subjects         | 1940                    |

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)                      | 2379 |
| From 65 to 84 years                       | 3252 |
| 85 years and over                         | 43   |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at multiple centers in 48 countries/regions between 17-SEP-2015 (first subject first visit) and 14-APR-2020 (last subject last visit).

### Pre-assignment

Screening details:

Overall, 13911 subjects were screened. Of them, 8177 subjects were screening failures and 5734 subjects were randomized. 60 subjects were prospectively excluded from the analyses due to GCP violations resulting in 5674 subjects in the full analysis set. 16 subjects did not take any study drug resulting in 5658 subjects who received study treatment.

### Period 1

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

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Finerenone |

Arm description:

Subjects received finerenone 10 mg or 20 mg once daily in addition to standard of care therapy

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Finerenone   |
| Investigational medicinal product code | BAY94-8862   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Oral tablet; starting dose at 10 mg for subjects with an eGFR between 25 to < 60 mL/min/1.73m<sup>2</sup> at the Screening Visit; starting dose at 20 mg for subjects with an eGFR ≥ 60 mL/min/1.73m<sup>2</sup> at the Screening Visit; dose could be up-titrated from Month 1 onwards or down-titrated at any time during the study; once daily in the morning, until the trial was completed provided there were no safety grounds for discontinuing treatment

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

Arm description:

Subjects received matching placebo once daily in addition to standard of care therapy

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

Dosage and administration details:

Matching placebo, oral tablet, once daily in the morning, until the trial was completed provided there were no safety grounds for discontinuing treatment

| <b>Number of subjects in period 1</b> | Finerenone | Placebo             |
|---------------------------------------|------------|---------------------|
| Started                               | 2833       | 2841                |
| Treated                               | 2827       | 2831 <sup>[1]</sup> |
| Completed                             | 2824       | 2832                |
| Not completed                         | 9          | 9                   |
| Consent withdrawn by subject          | 4          | 6                   |
| Lost to follow-up                     | 5          | 3                   |

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Notes:

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

Justification: Subjects were followed up regardless of having started treatment or not, and study completion (completion of period 1) is independent of administration of study treatment. A subject was considered as having completed the study if there was a contact with the subject after the end-of-study (EOS) notification or if the subject died.

## Baseline characteristics

### Reporting groups

|  |            |
|--|------------|
| Reporting group title  | Finerenone |
| Reporting group description:   |            |
| Subjects received finerenone 10 mg or 20 mg once daily in addition to standard of care therapy |            |
| Reporting group title  | Placebo    |
| Reporting group description:   |            |
| Subjects received matching placebo once daily in addition to standard of care therapy          |            |

| Reporting group values | Finerenone | Placebo | Total |
|------------------------|------------|---------|-------|
| Number of subjects     | 2833       | 2841    | 5674  |
| Age Categorical        |            |         |       |
| Units: Subjects        |            |         |       |

|   |                   |                   |      |
|---|-------------------|-------------------|------|
| Age Continuous                              |                   |                   |      |
| Units: years                                |                   |                   |      |
| arithmetic mean                             | 65.44             | 65.67             |      |
| standard deviation                          | ± 8.94            | ± 9.16            | -    |
| Gender Categorical                          |                   |                   |      |
| Units: Subjects                             |                   |                   |      |
| Female                                      | 880               | 811               | 1691 |
| Male  | 1953              | 2030              | 3983 |
| Race  |                   |                   |      |
| Units: Subjects                             |                   |                   |      |
| White                                       | 1777              | 1815              | 3592 |
| Black or African American                   | 140               | 124               | 264  |
| Asian                                       | 717               | 723               | 1440 |
| American Indian or Alaska Native            | 78                | 76                | 154  |
| Native Hawaiian or Other Pacific Islander   | 11                | 7                 | 18   |
| Not Reported                                | 9                 | 10                | 19   |
| Multiple                                    | 101               | 86                | 187  |
| Ethnicity                                   |                   |                   |      |
| Units: Subjects                             |                   |                   |      |
| Not Hispanic or Latino                      | 2376              | 2397              | 4773 |
| Hispanic or Latino                          | 447               | 431               | 878  |
| Not Reported                                | 10                | 13                | 23   |
| Urinary albumin-to-creatinine ratio (UACR)  |                   |                   |      |
| Units: milligram/gram (mg/g)                |                   |                   |      |
| median                                      | 832.72            | 867.01            |      |
| inter-quartile range (Q1-Q3)                | 441.00 to 1628.14 | 453.11 to 1644.58 | -    |
| Estimated glomerular filtration rate (eGFR) |                   |                   |      |
| Units: mL/min/1.73m <sup>2</sup>            |                   |                   |      |
| arithmetic mean                             | 44.36             | 44.32             |      |
| standard deviation                          | ± 12.54           | ± 12.57           | -    |

## End points

### End points reporting groups

|  |                         |
|--|-------------------------|
| Reporting group title  | Finerenone              |
| Reporting group description:   |                         |
| Subjects received finerenone 10 mg or 20 mg once daily in addition to standard of care therapy |                         |
| Reporting group title  | Placebo                 |
| Reporting group description:   |                         |
| Subjects received matching placebo once daily in addition to standard of care therapy          |                         |
| Subject analysis set title   | Full analysis set (FAS) |
| Subject analysis set type  | Full analysis           |
| Subject analysis set description:  |                         |
| The FAS comprised all randomized subjects (except those with critical GCP violations)          |                         |

### **Primary: The first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks, or renal death**

|   |   |
|---|---|
| End point title   | The first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks, or renal death |
| End point description:  |   |
| Count of subjects and time from randomization to the first occurrence of the primary renal composite outcome, onset of kidney failure, a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks, or renal death were evaluated. Number of subjects with the outcome event is reported as descriptive result and hazard ratio is reported as statistical analysis. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| From randomization up until the first occurrence of the primary renal composite endpoint, or censoring at the end of the study, with an average follow-up time of 32 months   |   |

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 2833            | 2841            |  |  |
| Units: Subjects             |                 |                 |  |  |
| number (not applicable)     | 504             | 600             |  |  |

### Statistical analyses

|  |                                  |
|--|----------------------------------|
| Statistical analysis title   | Primary renal composite endpoint |
| Statistical analysis description:  |                                  |
| A stratified Cox proportional hazards regression model was used to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval. |                                  |
| Comparison groups  | Finerenone v Placebo             |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 5674                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0014 <sup>[1]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.825                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.732                   |
| upper limit                             | 0.928                   |

Notes:

[1] - P-value from stratified log-rank test. Significance was considered to be achieved if p-value ≤ 0.03282695.

### **Secondary: The first occurrence of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure**

|                 |   |
|-----------------|---|
| End point title | The first occurrence of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure |
|-----------------|---|

End point description:

Count of subjects and time from randomization to the first occurrence of the key secondary cardiovascular (CV) composite outcome, CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for heart failure were evaluated. Number of subjects with the outcome event is reported as descriptive result and hazard ratio is reported as statistical analysis.

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

End point timeframe:

From randomization up until the first occurrence of the key secondary CV composite endpoint, or censoring at the end of the study, with an average of 32 months

| <b>End point values</b>     | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 2833            | 2841            |  |  |
| Units: Subjects             |                 |                 |  |  |
| number (not applicable)     | 367             | 420             |  |  |

### **Statistical analyses**

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | CV composite endpoint |
|-----------------------------------|-----------------------|

Statistical analysis description:

A stratified Cox proportional hazards regression model was used to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Finerenone v Placebo |
|-------------------|----------------------|



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 5674                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0339 <sup>[2]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.86                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.747                   |
| upper limit                             | 0.989                   |

Notes:

[2] - P-value from stratified log-rank test. Significance was considered to be achieved if p-value ≤ 0.04967388.

## Secondary: All-cause mortality

|  |                     |
|--|---------------------|
| End point title  | All-cause mortality |
| End point description:   |                     |
| Count of subjects and time from randomization until death due to any cause were evaluated. Number of subjects with outcome death is reported as descriptive result and hazard ratio is reported as statistical analysis. |                     |
| End point type   | Secondary           |
| End point timeframe:   |                     |
| From randomization up until death due to any cause, or censoring at the end of the study, with an average of 32 months   |                     |

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 2833            | 2841            |  |  |
| Units: Subjects             |                 |                 |  |  |
| number (not applicable)     | 219             | 244             |  |  |

## Statistical analyses

|  |                            |
|--|----------------------------|
| Statistical analysis title   | All-cause mortality        |
| Statistical analysis description:  |                            |
| A stratified Cox proportional hazards regression model was used to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval. |                            |
| Comparison groups  | Finerenone v Placebo       |
| Number of subjects included in analysis  | 5674                       |
| Analysis specification   | Pre-specified              |
| Analysis type  | superiority <sup>[3]</sup> |
| P-value  | = 0.2348 <sup>[4]</sup>    |
| Method   | Logrank                    |
| Parameter estimate   | Hazard ratio (HR)          |
| Point estimate   | 0.895                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.746   |
| upper limit         | 1.075   |

Notes:

[3] - As treatment effect on both primary and key secondary endpoint was significant, other secondary efficacy endpoints (i.e. all-cause mortality, all-cause hospitalization, change in UACR from baseline to Month 4, and secondary renal composite endpoint) were tested hierarchically, starting with all-cause mortality. As treatment effect on all-cause mortality was not significant, all other endpoints were tested in an exploratory manner.

[4] - P-value from stratified log-rank test. Significance was considered to be achieved if p-value  $\leq$  0.04967388.

## Secondary: All-cause hospitalization

|                 |                           |
|-----------------|---------------------------|
| End point title | All-cause hospitalization |
|-----------------|---------------------------|

End point description:

Count of subjects and time from randomization to the first occurrence of a hospitalization event were evaluated. Number of subjects with the event is reported as descriptive result and hazard ratio is reported as statistical analysis.

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

End point timeframe:

From randomization up until the first occurrence of the hospitalization due to any cause, or censoring at the end of the study, with an average of 32 months

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 2833            | 2841            |  |  |
| Units: Subjects             |                 |                 |  |  |
| number (not applicable)     | 1263            | 1321            |  |  |

## Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | All-cause hospitalization |
|----------------------------|---------------------------|

Statistical analysis description:

A stratified Cox proportional hazards regression model was used to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Finerenone v Placebo       |
| Number of subjects included in analysis | 5674                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| P-value                                 | = 0.1623 <sup>[6]</sup>    |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.946                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.876   |
| upper limit         | 1.022   |

Notes:

[5] - As treatment effect on both primary and key secondary endpoint was significant, other secondary efficacy endpoints (i.e. all-cause mortality, all-cause hospitalization, change in UACR from baseline to Month 4, and secondary renal composite endpoint) were tested hierarchically, starting with all-cause mortality. As treatment effect on all-cause mortality was not significant, all other endpoints were tested in an exploratory manner.

[6] - P-value from stratified log-rank test.

## Secondary: Change in urinary albumin-to-creatinine ratio (UACR) from baseline to Month 4

|                 |   |
|-----------------|---|
| End point title | Change in urinary albumin-to-creatinine ratio (UACR) from baseline to Month 4 |
|-----------------|---|

End point description:

First morning void urine samples were collected to evaluate the urinary albumin-to-creatinine ratio (UACR). Month 4 was the visit closest to day 120 within a time window of  $120 \pm 30$  days after randomization. If no measurements were available in this time window, the subject was excluded from this analysis. Ratio of UACR at Month 4 to UACR at baseline is reported as the change. The analysis was performed on the subjects in FAS with measurements available within the time window of Month 4.

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

End point timeframe:

From baseline up until Month 4

| End point values                             | Finerenone             | Placebo                |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                  | 2711                   | 2705                   |  |  |
| Units: Ratio                                 |                        |                        |  |  |
| least squares mean (confidence interval 95%) | 0.655 (0.637 to 0.673) | 0.952 (0.927 to 0.979) |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change in UACR from baseline to Month 4 |
| Comparison groups                       | Finerenone v Placebo                    |
| Number of subjects included in analysis | 5416                                    |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[7]</sup>              |
| P-value                                 | < 0.0001 <sup>[8]</sup>                 |
| Method                                  | ANCOVA                                  |
| Parameter estimate                      | Ratio of least squares means            |
| Point estimate                          | 0.688                                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.662   |
| upper limit         | 0.715   |

Notes:

[7] - As treatment effect on both primary and key secondary endpoint was significant, other secondary efficacy endpoints (i.e. all-cause mortality, all-cause hospitalization, change in UACR from baseline to Month 4, and secondary renal composite endpoint) were tested hierarchically, starting with all-cause mortality. As treatment effect on all-cause mortality was not significant, all other endpoints were tested in an exploratory manner.

[8] - P-value from F-test of equal means between the treatment groups.

### **Secondary: The first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease in eGFR of $\geq 57\%$ from baseline over at least 4 weeks, or renal death**

|                 |  |
|-----------------|--|
| End point title | The first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease in eGFR of $\geq 57\%$ from baseline over at least 4 weeks, or renal death |
|-----------------|--|

End point description:

Count of subjects and time from randomization to the first occurrence of the secondary renal composite outcome, onset of kidney failure, a sustained decrease in eGFR of  $\geq 57\%$  from baseline over at least 4 weeks, or renal death were evaluated. Number of subjects with the outcome event is reported as descriptive result and hazard ratio is reported as statistical analysis.

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

End point timeframe:

From randomization up until the first occurrence of the composite primary endpoint, or censoring at the end of the study, with an average of 32 months

| <b>End point values</b>     | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 2833            | 2841            |  |  |
| Units: Subjects             |                 |                 |  |  |
| number (not applicable)     | 252             | 326             |  |  |

### **Statistical analyses**

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Secondary renal composite endpoint |
|-----------------------------------|------------------------------------|

Statistical analysis description:

A stratified Cox proportional hazards regression model was used to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Finerenone v Placebo       |
| Number of subjects included in analysis | 5674                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[9]</sup> |
| P-value                                 | = 0.0012 <sup>[10]</sup>   |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.763                      |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.648   |
| upper limit         | 0.9     |

Notes:

[9] - As treatment effect on both primary and key secondary endpoint was significant, other secondary efficacy endpoints (i.e. all-cause mortality, all-cause hospitalization, change in UACR from baseline to Month 4, and secondary renal composite endpoint) were tested hierarchically, starting with all-cause mortality. As treatment effect on all-cause mortality was not significant, all other endpoints were tested in an exploratory manner.

[10] - P-value from stratified log-rank test.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

After the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug, with an average treatment duration of 27 months

Adverse event reporting additional description:

Adverse event reporting for the numbers of deaths (all causes) considers all deaths in the safety analysis set (comprised all randomized subjects who took at least 1 dose of study drug [except those with critical GCP violations]) that occurred at any time during the study after the first dose of study drug (with an average duration of 32 months).

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
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| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Finerenone |
|-----------------------|------------|

Reporting group description:

Subjects received finerenone 10 mg or 20 mg once daily in addition to standard of care therapy

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

Reporting group description:

Subjects received matching placebo once daily in addition to standard of care therapy

| Serious adverse events  | Finerenone          | Placebo             |  |
|---|---------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                     |                     |  |
| subjects affected / exposed   | 902 / 2827 (31.91%) | 971 / 2831 (34.30%) |  |
| number of deaths (all causes)                                       | 220                 | 249                 |  |
| number of deaths resulting from adverse events                      | 31                  | 51                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                     |  |
| Acute myeloid leukaemia   |                     |                     |  |
| subjects affected / exposed   | 0 / 2827 (0.00%)    | 2 / 2831 (0.07%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 2               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 1               |  |
| Adenocarcinoma  |                     |                     |  |
| subjects affected / exposed   | 1 / 2827 (0.04%)    | 1 / 2831 (0.04%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               |  |
| Adenocarcinoma gastric  |                     |                     |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenocarcinoma of colon                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenoma benign                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adrenal adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell lymphoma stage IV                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign salivary gland neoplasm                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer recurrent                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                       | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Bladder neoplasm                                  |                  |                  |  |
| subjects affected / exposed                       | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all   | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Bladder squamous cell carcinoma stage unspecified |                  |                  |  |
| subjects affected / exposed                       | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma               |                  |                  |  |
| subjects affected / exposed                       | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| 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                       | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Breast cancer                                     |                  |                  |  |
| subjects affected / exposed                       | 4 / 2827 (0.14%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all   | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Breast neoplasm                                   |                  |                  |  |
| subjects affected / exposed                       | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all   | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Cholangiocarcinoma                                |                  |                  |  |
| subjects affected / exposed                       | 1 / 2827 (0.04%) | 0 / 2831 (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 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Colon cancer stage IV                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma recurrent         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Endometrial adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibroadenoma of breast                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrosarcoma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastric cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastrointestinal carcinoma                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemangioma                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal squamous cell carcinoma               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lentigo maligna                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lipoma  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung adenocarcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung carcinoma cell type unspecified stage IV   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung squamous cell carcinoma stage IV           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphoma  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant neoplasm of ampulla of Vater          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to bone                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to lymph nodes                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to spine                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic malignant melanoma                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelodysplastic syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasal cavity cancer                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neoplasm  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neoplasm prostate                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma of the skin            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Oesophageal carcinoma                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oropharyngeal cancer                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Pancreatic carcinoma metastatic                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Penile cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plasma cell myeloma                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer metastatic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenocarcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Renal cancer                                    |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                      | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Sarcoma  |                  |                  |  |
| subjects affected / exposed                      | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 1            | 0 / 0            |  |
| Small cell lung cancer                           |                  |                  |  |
| subjects affected / exposed                      | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 1            |  |
| Squamous cell carcinoma of lung                  |                  |                  |  |
| subjects affected / exposed                      | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of skin                  |                  |                  |  |
| subjects affected / exposed                      | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all  | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the oral cavity       |                  |                  |  |
| subjects affected / exposed                      | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the tongue            |                  |                  |  |
| subjects affected / exposed                      | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Superficial spreading melanoma stage unspecified |                  |                  |  |
| subjects affected / exposed                      | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Tongue neoplasm malignant stage                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| unspecified                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsil cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transitional cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulval cancer stage 0                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung cancer metastatic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic renal cell carcinoma                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal stromal tumour                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to spleen                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal cancer metastatic                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal cancer metastatic                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Breast cancer metastatic                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected neoplasm                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cancer pain                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung neoplasm malignant                         |                  |                  |  |



|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 9 / 2827 (0.32%)  | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2            |  |
| Metastases to central nervous system            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pancreatic carcinoma stage IV                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Small cell lung cancer metastatic               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Prostate cancer                                 |                   |                  |  |
| subjects affected / exposed                     | 13 / 2827 (0.46%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Monoclonal gammopathy                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Benign pancreatic neoplasm                      |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Brain neoplasm                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Malignant urinary tract neoplasm                |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colorectal cancer                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland neoplasm                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pituitary tumour benign                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic neoplasm                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung neoplasm                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tongue neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral neoplasm                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sarcoma metastatic                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Tumour rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant neoplasm of unknown primary site      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Hepatobiliary cancer                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intraductal proliferative breast lesion         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clear cell renal cell carcinoma                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ductal adenocarcinoma of pancreas               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angiomyofibroblastoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenocarcinoma metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic dissection                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriovenous fistula                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure fluctuation                      |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Circulatory collapse                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Embolism venous                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haematoma                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertension                                    |                   |                   |  |
| subjects affected / exposed                     | 15 / 2827 (0.53%) | 23 / 2831 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 26            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive crisis                             |                   |                   |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypotension                                     |                   |                   |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 3 / 7             | 2 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypovolaemic shock                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Intermittent claudication                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphoedema                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant hypertension                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Temporal arteritis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thromboangiitis obliterans                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis superficial                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shock haemorrhagic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dry gangrene                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery aneurysm                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery occlusion                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive emergency                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive urgency                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Venous occlusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extremity necrosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral embolism                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic vascular disorder                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Microangiopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| 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 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Aortic valve replacement                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriovenous fistula operation                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac pacemaker insertion                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystectomy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery bypass                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot amputation                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemodialysis                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip arthroplasty                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hysterectomy                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Insertion of ambulatory peritoneal catheter     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Knee arthroplasty                               |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leg amputation                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metatarsal excision                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myomectomy                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrectomy                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parathyroidectomy                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Physiotherapy                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pterygium operation                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhinoplasty                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal decompression                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tenotomy  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toe amputation                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transurethral prostatectomy                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia repair                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine prolapse repair                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitrectomy                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenectomy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac pacemaker replacement                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Implantable defibrillator insertion             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary angioplasty                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal fusion surgery                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radical prostatectomy                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus management                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transurethral bladder resection                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac rehabilitation therapy                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Continuous positive airway pressure             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephroureterectomy                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreaticosplenectomy                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polypectomy                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Maxillofacial operation                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Corneal transplant                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus operation                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder neck operation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral dilation procedure                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc operation                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rehabilitation therapy                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dialysis device insertion                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin neoplasm excision                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot operation                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amputation                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthrodesis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colectomy                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon operation                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye operation                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oophorectomy                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatectomy                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrectomy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric bypass                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrocele operation                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal operation                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nail operation                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin graft                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal operation                                |                  |                  |  |



|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Wound treatment                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bladder polypectomy                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cataract operation                              |                  |                   |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 12 / 2831 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aneurysm repair                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bowel preparation                               |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Retinopexy                                      |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intraocular lens implant                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Vascular graft                                  |                  |                   |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Internal fixation of spine                           |                  |                  |  |
| subjects affected / exposed                          | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Bile duct stent removal                              |                  |                  |  |
| subjects affected / exposed                          | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Gastric banding reversal                             |                  |                  |  |
| subjects affected / exposed                          | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Therapeutic nerve ablation                           |                  |                  |  |
| subjects affected / exposed                          | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Peripheral artery bypass                             |                  |                  |  |
| subjects affected / exposed                          | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Large intestinal polypectomy                         |                  |                  |  |
| subjects affected / exposed                          | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Metabolic surgery                                    |                  |                  |  |
| subjects affected / exposed                          | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Asthenia   |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chest discomfort                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chest pain                                      |                   |                   |  |
| subjects affected / exposed                     | 13 / 2827 (0.46%) | 18 / 2831 (0.64%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 20            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Death   |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 4 / 2831 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 4             |  |
| Fatigue   |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gait disturbance                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Generalised oedema                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypothermia                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malaise   |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mass  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 8 / 2827 (0.28%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue inflammation                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Swelling face                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral swelling                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hernia pain                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema due to renal disease                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammation                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device intolerance                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular stent stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple organ dysfunction syndrome             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Drug hypersensitivity                           |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Social circumstances                            |                  |                   |  |
| Social stay hospitalisation                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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        |                  |                   |  |
| Balanoposthitis                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Benign prostatic hyperplasia                    |                  |                   |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 10 / 2831 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dysfunctional uterine bleeding                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Endometrial hyperplasia                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Metrorrhagia                                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ovarian cyst                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Uterine haemorrhage                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Uterine polyp                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Vaginal haemorrhage                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Prostatomegaly                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Endometrial thickening                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Testicular mass                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| 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                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Acute respiratory failure                       |                  |                   |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 15 / 2831 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2             |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Aspiration                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Asthma  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 6 / 2831 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Bronchitis chronic                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic obstructive pulmonary disease           |                   |                   |  |
| subjects affected / exposed                     | 14 / 2827 (0.50%) | 12 / 2831 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 21            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Chronic respiratory failure                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 8 / 2827 (0.28%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea at rest                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea exertional                             |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Emphysema                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epistaxis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Interstitial lung disease                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Laryngeal oedema                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal stenosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngeal oedema                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleurisy  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia aspiration                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary congestion                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 8 / 2827 (0.28%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary hypertension                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary oedema                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory distress                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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 / 2827 (0.18%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Sleep apnoea syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vocal cord polyp                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wheezing  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Restrictive pulmonary disease                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vocal cord cyst                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchopneumopathy                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary mass                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal dysplasia                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiglottic cyst                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal mass                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary hilum mass                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive airways disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Alcohol abuse                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anxiety   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Insomnia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mania   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental status changes                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar disorder                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Major depression                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device dislocation                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary colic                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis acute                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 9 / 2831 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cholecystitis chronic                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cholelithiasis                                  |                   |                  |  |
| subjects affected / exposed                     | 12 / 2827 (0.42%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cholestasis                                     |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatic cirrhosis                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Hepatic function abnormal                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatitis                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatitis acute                                 |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatitis alcoholic                             |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice cholestatic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary dilatation                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic lesion                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug-induced liver injury                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Alanine aminotransferase increased              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aspartate aminotransferase increased            |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biopsy kidney                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood creatine phosphokinase increased          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood creatine phosphokinase MB increased       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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 / 2827 (0.04%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood glucose increased                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood potassium increased                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure increased                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colonoscopy                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endoscopy small intestine                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gamma-glutamyltransferase increased             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glomerular filtration rate decreased            |                  |                  |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart rate increased                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight decreased                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ejection fraction decreased                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Protein urine present                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac pacemaker evaluation                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Computerised tomogram abdomen                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac stress test abnormal                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Troponin T increased                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood alkaline phosphatase increased            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Light chain analysis increased                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anticoagulation drug level above therapeutic    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriogram                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammatory marker increased                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza A virus test positive                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiovascular examination                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arteriogram                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver function test increased                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angiocardiogram                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Accident  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Accidental overdose                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acetabulum fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol poisoning                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Burns second degree                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clavicle fracture                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dislocation of vertebra                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial bones fracture                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 9 / 2831 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibula fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Forearm fracture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand fracture                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heat stroke                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incisional hernia                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intentional overdose                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Poisoning deliberate                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation proctitis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue injury                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord injury cervical                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Spinal fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sternal fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Tendon injury                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tibia fracture                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulna fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thoracic vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle strain                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound necrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammation of wound                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriovenous fistula site complication         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post concussion syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin laceration                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incision site haematoma                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament injury                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skull fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chest injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound complication                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shunt malfunction                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural inflammation                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal wound dehiscence                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Craniocerebral injury                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac contusion                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic haemothorax                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated incisional hernia                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular access malfunction                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ocular procedural complication                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Dermoid cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Factor VIII deficiency                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Phimosis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Truncus arteriosus persistent                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac disorders                               |                  |                  |  |
| Angina pectoris                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina unstable                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic valve disease mixed                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic valve stenosis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arrhythmia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriosclerosis coronary artery                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial flutter                                  |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular block                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bradycardia                                     |                  |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac arrest                                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac asthma                                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac failure                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 10 / 2831 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac failure acute                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac failure chronic                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac failure congestive                      |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 8 / 2831 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardio-respiratory arrest                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cardiogenic shock                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiomyopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery disease                         |                  |                  |  |
| subjects affected / exposed                     | 8 / 2827 (0.28%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive heart disease                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular failure                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myocardial ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial thrombosis                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular dysfunction                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic valve calcification                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute coronary syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bifascicular block                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mitral valve disease                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute left ventricular failure                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stress cardiomyopathy                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiorenal syndrome                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus node dysfunction                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic mitral regurgitation                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Alcohol induced persisting dementia             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Altered state of consciousness                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aphasia   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brown-Sequard syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carpal tunnel syndrome                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cerebral infarction                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral ischaemia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrovascular disorder                        |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervicobrachial syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cranial nerve palsies multiple                  |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Diabetic neuropathy                             |                  |                   |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dizziness                                       |                  |                   |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 10 / 2831 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 2 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Drop attacks                                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dysarthria                                      |                  |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Epilepsy  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Facial paralysis                                |                  |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Headache  |                  |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hemiparesis                                     |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| IIIrd nerve paralysis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lethargy  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelopathy                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuralgia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuropathy peripheral                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyneuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post herpetic neuralgia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiculopathy                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sciatica  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subarachnoid haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Syncope   |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 12 / 2827 (0.42%) | 22 / 2831 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 2 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transient ischaemic attack                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vertebrobasilar insufficiency                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Brain oedema                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Carotid artery occlusion                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vertebral artery occlusion                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arachnoid cyst                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Balance disorder                                |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lacunar infarction                              |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial paresis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurodegenerative disorder                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral disorder                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroglycopenia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrovascular insufficiency                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral vasoconstriction                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic cerebral infarction                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mononeuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular encephalopathy                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral arteriosclerosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid arteriosclerosis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombotic cerebral infarction                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral microangiopathy                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia with Lewy bodies                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxic-ischaemic encephalopathy                |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Secondary cerebellar degeneration               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lumbosacral radiculopathy                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebral vascular occlusion                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Post stroke epilepsy                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hemianaesthesia                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angiopathic neuropathy                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (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                     | 14 / 2827 (0.50%) | 19 / 2831 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Febrile neutropenia                             |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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                     | 5 / 2827 (0.18%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy mediastinal                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Microcytic anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Normocytic anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrogenic anaemia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood loss anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune thrombocytopenia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Deafness neurosensory                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear pain  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tinnitus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tympanic membrane perforation                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo   |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 2827 (0.11%)  | 4 / 2831 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vertigo positional                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vestibular disorder                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Deafness unilateral                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| 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                     | 2 / 2827 (0.07%)  | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Eye disorders                                   |                   |                   |  |
| Blindness                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cataract  |                   |                   |  |
| subjects affected / exposed                     | 19 / 2827 (0.67%) | 12 / 2831 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 22            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cataract diabetic                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cataract subcapsular                            |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic retinal oedema                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic retinopathy                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ectropion                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorder                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye haemorrhage                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 6 / 2827 (0.21%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lens dislocation                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular oedema                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Open angle glaucoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic disc haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papilloedema                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pterygium                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal detachment                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinopathy                                     |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual impairment                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitreous haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular hole                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulcerative keratitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhegmatogenous retinal detachment               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular fibrosis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tractional retinal detachment                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal pain                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fistula                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Change of bowel habit                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dental caries                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 6 / 2831 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 7            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea haemorrhagic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal haemorrhagic            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal polyp                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Duodenal ulcer perforation                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Duodenitis haemorrhagic                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric polyps                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer perforation                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis erosive                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis haemorrhagic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroduodenal ulcer                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorder                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 13 / 2827 (0.46%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Gastrointestinal necrosis                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Haematemesis                                    |                   |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Haematochezia                                   |                   |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Haemorrhoids                                    |                   |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ileus   |                   |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Impaired gastric emptying                       |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| 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                     | 1 / 2827 (0.04%)  | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal angina                               |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal obstruction                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal perforation                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Melaena   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal achalasia                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal ulcer haemorrhage                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic cyst                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 8 / 2831 (0.28%) |  |
| occurrences causally related to treatment / all | 1 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pancreatitis chronic                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Proctitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal polyp                                    |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland calculus                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subileus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine polyp                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chilaiditi's syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedematous pancreatitis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal strangulated hernia                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoidal haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varices oesophageal                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faecaloma                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal ulcer haemorrhage              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcoholic pancreatitis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retroperitoneal haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric mucosal lesion                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal motility disorder              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated umbilical hernia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic duct stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic erosive gastritis                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Functional gastrointestinal disorder                |                  |                  |  |
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Retroperitoneal mass                                |                  |                  |  |
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Strangulated umbilical hernia                       |                  |                  |  |
| subjects affected / exposed                         | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Intra-abdominal fluid collection                    |                  |                  |  |
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Obstructive pancreatitis                            |                  |                  |  |
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Gastrointestinal vascular malformation haemorrhagic |                  |                  |  |
| subjects affected / exposed                         | 1 / 2827 (0.04%) | 0 / 2831 (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 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| 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 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blister   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Decubitus ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermal cyst                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis allergic                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis bullous                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis herpetiformis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug eruption                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ecchymosis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eczema  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkeratosis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ingrowing nail                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parapsoriasis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pemphigoid                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Purpura   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin disorder                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin necrosis                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin ulcer                                      |                   |                   |  |
| subjects affected / exposed                     | 9 / 2827 (0.32%)  | 16 / 2831 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stasis dermatitis                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stevens-Johnson syndrome                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Neuropathic ulcer                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diabetic foot                                   |                   |                   |  |
| subjects affected / exposed                     | 13 / 2827 (0.46%) | 18 / 2831 (0.64%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal and urinary disorders                     |                   |                   |  |
| Azotaemia                                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Calculus bladder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus urinary                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chromaturia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis ulcerative                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysuria   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glomerular vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intercapillary glomerulosclerosis               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrolithiasis                                 |                  |                  |  |
| subjects affected / exposed                     | 6 / 2827 (0.21%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephropathy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephropathy toxic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrosclerosis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 9 / 2831 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nocturia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Proteinuria                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal artery stenosis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cyst                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 2 / 7            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal haemorrhage                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal tubular acidosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 6 / 2827 (0.21%)  | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tubulointerstitial nephritis                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 2 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary bladder polyp                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive nephropathy                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bladder cyst                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract obstruction                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diabetic nephropathy                            |                   |                   |  |
| subjects affected / exposed                     | 18 / 2827 (0.64%) | 16 / 2831 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal mass                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal impairment                                |                   |                   |  |

|   |                   |                   |
|---|-------------------|-------------------|
| subjects affected / exposed                     | 8 / 2827 (0.28%)  | 8 / 2831 (0.28%)  |
| occurrences causally related to treatment / all | 0 / 8             | 1 / 10            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Chronic kidney disease                          |                   |                   |
| subjects affected / exposed                     | 12 / 2827 (0.42%) | 22 / 2831 (0.78%) |
| occurrences causally related to treatment / all | 1 / 12            | 0 / 26            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Urethral stenosis                               |                   |                   |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Acute kidney injury                             |                   |                   |
| subjects affected / exposed                     | 56 / 2827 (1.98%) | 51 / 2831 (1.80%) |
| occurrences causally related to treatment / all | 10 / 63           | 6 / 55            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |
| Bladder outlet obstruction                      |                   |                   |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Perinephritis                                   |                   |                   |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| End stage renal disease                         |                   |                   |
| subjects affected / exposed                     | 5 / 2827 (0.18%)  | 4 / 2831 (0.14%)  |
| occurrences causally related to treatment / all | 0 / 5             | 1 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Ureterolithiasis                                |                   |                   |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 3 / 2831 (0.11%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Subcapsular renal haematoma                     |                   |                   |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Goitre  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperthyroidism                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pituitary-dependent Cushing's syndrome          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroiditis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid mass                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Back disorder                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bursitis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical spinal stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Costochondritis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Flank pain                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (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                     | 5 / 2827 (0.18%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar spinal stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 7 / 2831 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal pain                            |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Neck pain                                       |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Neuropathic arthropathy                         |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Osteitis  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Osteoarthritis                                  |                   |                  |  |
| subjects affected / exposed                     | 11 / 2827 (0.39%) | 8 / 2831 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Osteoarthropathy                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Osteonecrosis                                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pain in extremity                               |                   |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Polymyalgia rheumatica                          |                   |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Rhabdomyolysis                                  |                  |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Rheumatoid arthritis                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Rotator cuff syndrome                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Spinal osteoarthritis                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Tenosynovitis                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Musculoskeletal disorder                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intervertebral disc protrusion                  |                  |                   |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 13 / 2831 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Musculoskeletal chest pain                      |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma muscle                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Connective tissue inflammation                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot deformity                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc degeneration                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylolisthesis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteonecrosis of jaw                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue necrosis                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal instability                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb mass                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal wall abscess                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Atypical pneumonia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacteraemia                                     |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis                                      |                   |                   |  |
| subjects affected / exposed                     | 9 / 2827 (0.32%)  | 13 / 2831 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 1 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Campylobacter gastroenteritis                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Carbuncle                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis                                      |                   |                   |  |
| subjects affected / exposed                     | 26 / 2827 (0.92%) | 22 / 2831 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 30            | 0 / 23            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Chronic sinusitis                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clostridium difficile colitis                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cystitis  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dengue fever                                    |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic gangrene                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear infection                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endophthalmitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epididymitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiglottitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 11 / 2827 (0.39%) | 14 / 2831 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Fournier's gangrene                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gangrene  |                   |                   |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Gastroenteritis                                 |                   |                   |  |
| subjects affected / exposed                     | 9 / 2827 (0.32%)  | 13 / 2831 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 1 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis salmonella                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis viral                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hepatitis B                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hepatitis viral                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Herpes zoster                                   |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kidney infection                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Labyrinthitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leptospirosis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 7 / 2827 (0.25%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lower respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mastoiditis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oesophageal candidiasis                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Orchitis  |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis                                   |                   |                   |  |
| subjects affected / exposed                     | 14 / 2827 (0.50%) | 12 / 2831 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Osteomyelitis chronic                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Otitis externa                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Otitis media                                    |                   |                   |  |

|   |                   |                    |  |
|---|-------------------|--------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Paronychia                                      |                   |                    |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Periodontitis                                   |                   |                    |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Peritonitis                                     |                   |                    |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pharyngitis streptococcal                       |                   |                    |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pneumonia                                       |                   |                    |  |
| subjects affected / exposed                     | 70 / 2827 (2.48%) | 103 / 2831 (3.64%) |  |
| occurrences causally related to treatment / all | 0 / 75            | 0 / 115            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 5              |  |
| Pneumonia respiratory syncytial viral           |                   |                    |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pneumonia streptococcal                         |                   |                    |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Postoperative wound infection                   |                   |                    |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatic abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary tuberculosis                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis chronic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyonephrosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 15 / 2827 (0.53%) | 17 / 2831 (0.60%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Septic shock                                    |                   |                   |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 4             |  |
| Sinusitis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Splenic abscess                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Subcutaneous abscess                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tracheobronchitis                               |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urethritis                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection                         |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 21 / 2827 (0.74%) | 23 / 2831 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 22            | 0 / 30            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral infection                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral pericarditis                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral tracheitis                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Wound infection                                 |                   |                   |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%)  | 3 / 2831 (0.11%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oral infection                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urosepsis                                       |                   |                   |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 9             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anal abscess                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rectal abscess                                  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal sepsis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelocystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenic sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonsillitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Groin abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Burn infection                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma infection                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chest wall abscess                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary sepsis                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 2827 (0.18%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Febrile infection                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia urinary tract infection             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal tuberculosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterococcal sepsis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile infection                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis infectious                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Klebsiella bacteraemia                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viraemia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute hepatitis B                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral discitis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot infection                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 2827 (0.14%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal abscess                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Borrelia infection                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory syncytial virus infection           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes ophthalmic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis bacterial                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue infection                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection staphylococcal          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory tract infection                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 4 / 2831 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infective spondylitis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stoma site infection                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermo-hypodermatitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural sepsis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| H1N1 influenza                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device related sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infective exacerbation of bronchiectasis        |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected seroma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Medical device site joint infection             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected bite                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine infection                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephritis bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bullous erysipelas                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%) | 5 / 2831 (0.18%) |  |
| occurrences causally related to treatment / all | 1 / 7            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus                               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 10 / 2827 (0.35%) | 16 / 2831 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diabetes mellitus inadequate control            |                   |                   |  |
| subjects affected / exposed                     | 12 / 2827 (0.42%) | 19 / 2831 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diabetic ketoacidosis                           |                   |                   |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fluid overload                                  |                   |                   |  |
| subjects affected / exposed                     | 7 / 2827 (0.25%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 1 / 9             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fluid retention                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gout  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 7 / 2831 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypercalcaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperglycaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 17 / 2827 (0.60%) | 23 / 2831 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 26            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperkalaemia                                   |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 42 / 2827 (1.49%) | 12 / 2831 (0.42%) |  |
| occurrences causally related to treatment / all | 26 / 45           | 5 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperosmolar state                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypervolaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypocalcaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypoglycaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 21 / 2827 (0.74%) | 31 / 2831 (1.10%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 33            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypoglycaemia unawareness                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypokalaemia                                    |                   |                   |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%)  | 5 / 2831 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypomagnesaemia                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 1 / 2831 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyponatraemia                                   |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 2827 (0.28%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 12           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoproteinaemia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2827 (0.11%) | 2 / 2831 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ketoacidosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic acidosis                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%) | 3 / 2831 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tumour lysis syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calciphylaxis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%) | 0 / 2831 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%) | 1 / 2831 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Diabetic complication                           |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malnutrition                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2827 (0.04%)  | 0 / 2831 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Decreased appetite                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2827 (0.00%)  | 2 / 2831 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperglycaemic hyperosmolar nonketotic syndrome |                   |                   |  |
| subjects affected / exposed                     | 2 / 2827 (0.07%)  | 4 / 2831 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Type 2 diabetes mellitus                        |                   |                   |  |
| subjects affected / exposed                     | 14 / 2827 (0.50%) | 22 / 2831 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 28            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diabetic metabolic decompensation               |                   |                   |  |
| subjects affected / exposed                     | 12 / 2827 (0.42%) | 14 / 2831 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

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

| Non-serious adverse events                            | Finerenone           | Placebo              |  |
|---|----------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                      |                      |  |
| subjects affected / exposed                           | 1602 / 2827 (56.67%) | 1584 / 2831 (55.95%) |  |
| Investigations  |                      |                      |  |
| Glomerular filtration rate decreased                  |                      |                      |  |
| subjects affected / exposed                           | 177 / 2827 (6.26%)   | 130 / 2831 (4.59%)   |  |
| occurrences (all)                                     | 225                  | 146                  |  |

|   |  |  |  |
|---|--|--|--|
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 200 / 2827 (7.07%)<br>229                                  | 262 / 2831 (9.25%)<br>323                                  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 143 / 2827 (5.06%)<br>165                                  | 147 / 2831 (5.19%)<br>162                                  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 201 / 2827 (7.11%)<br>218                                  | 177 / 2831 (6.25%)<br>196                                  |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 183 / 2827 (6.47%)<br>216                                  | 303 / 2831<br>(10.70%)<br>359                              |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                       | 128 / 2827 (4.53%)<br>146<br><br>183 / 2827 (6.47%)<br>216 | 162 / 2831 (5.72%)<br>179<br><br>188 / 2831 (6.64%)<br>224 |  |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 142 / 2827 (5.02%)<br>163<br><br>175 / 2827 (6.19%)<br>187 | 145 / 2831 (5.12%)<br>157<br><br>170 / 2831 (6.00%)<br>182 |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                  | 127 / 2827 (4.49%)<br>140<br><br>241 / 2827 (8.52%)<br>368 | 142 / 2831 (5.02%)<br>188<br><br>250 / 2831 (8.83%)<br>391 |  |

|   |                               |                           |  |
|---|-------------------------------|---------------------------|--|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 181 / 2827 (6.40%)<br>274     | 185 / 2831 (6.53%)<br>262 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 168 / 2827 (5.94%)<br>215     | 185 / 2831 (6.53%)<br>259 |  |
| Metabolism and nutrition disorders  |                               |                           |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                     | 422 / 2827<br>(14.93%)<br>634 | 212 / 2831 (7.49%)<br>281 |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 137 / 2827 (4.85%)<br>212     | 173 / 2831 (6.11%)<br>299 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 03 May 2017      | The major modifications specified in Amendment 3 were an increase of study duration and site numbers to account for lower than expected recruitment rate, amended re-screening rules, a modification of an exclusion criterion to allow randomization of subjects with a recent CV disease episode, and the addition of the definition of the endpoint "kidney failure".  |
| 26 February 2019 | The main modification due to Amendment 4 was to allow performing the post-treatment Visit as a telephone contact, to specify baseline values for subjects who did not immediately start with study drug treatment, to increase the time window after last study drug administration from 3 to 30 days for on-treatment analyses to better reflect the more protracted nature of the development and diagnosis of clinical outcome events of interest in relation to treatment exposure, and to specify the definition of treatment emergent AEs and interruptions of study treatment. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31655812>

<http://www.ncbi.nlm.nih.gov/pubmed/33264825>

<http://www.ncbi.nlm.nih.gov/pubmed/33198491>