



## Clinical trial results:

**A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction 40% (LVEF 40%).**

### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2020-000306-29                                  |
| Trial protocol           | DE GB DK AT HU BG PT NL SK GR CZ LT FI LV IT RO |
| Global end of trial date | 14 June 2024                                    |

### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 23 October 2025  |
| First version publication date | 15 June 2025   |
| Version creation reason        | <ul style="list-style-type: none"><li>New data added to full data set to update the Adverse event data</li></ul> |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 20103 |
|-----------------------|-------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04435626 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368   |
| Public contact               | Bayer Clinical Trials Contact, Bayer AG, 0049 30300139003, clinical-trials-contact@bayer.com |
| Scientific contact           | Bayer Clinical Trials Contact, Bayer AG, 0049 30300139003, 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 June 2024 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 14 June 2024 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the superiority of finerenone to placebo in reducing the rate of the composite CV endpoint of CV death and total heart failure (HF) events in HF patients (LVEF  $\geq$ 40%).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice (GCP). Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative 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: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 14 September 2020 |
| 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 | Netherlands: 64    |
| Country: Number of subjects enrolled | Poland: 259        |
| Country: Number of subjects enrolled | Portugal: 88       |
| Country: Number of subjects enrolled | Romania: 193       |
| Country: Number of subjects enrolled | Slovakia: 262      |
| Country: Number of subjects enrolled | Spain: 353         |
| Country: Number of subjects enrolled | United Kingdom: 99 |
| Country: Number of subjects enrolled | Austria: 73        |
| Country: Number of subjects enrolled | Bulgaria: 275      |
| Country: Number of subjects enrolled | Czechia: 206       |
| Country: Number of subjects enrolled | Denmark: 79        |
| Country: Number of subjects enrolled | Finland: 20        |
| Country: Number of subjects enrolled | Germany: 20        |
| Country: Number of subjects enrolled | Hungary: 267       |
| Country: Number of subjects enrolled | Italy: 227         |
| Country: Number of subjects enrolled | Latvia: 65         |
| Country: Number of subjects enrolled | Lithuania: 100     |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Australia: 32           |
| Country: Number of subjects enrolled | Israel: 181             |
| Country: Number of subjects enrolled | New Zealand: 40         |
| Country: Number of subjects enrolled | Russian Federation: 300 |
| Country: Number of subjects enrolled | Ukraine: 327            |
| Country: Number of subjects enrolled | China: 538              |
| Country: Number of subjects enrolled | India: 28               |
| Country: Number of subjects enrolled | Japan: 286              |
| Country: Number of subjects enrolled | Korea, Republic of: 74  |
| Country: Number of subjects enrolled | Malaysia: 57            |
| Country: Number of subjects enrolled | Canada: 116             |
| Country: Number of subjects enrolled | United States: 355      |
| Country: Number of subjects enrolled | Argentina: 211          |
| Country: Number of subjects enrolled | Brazil: 185             |
| Country: Number of subjects enrolled | Colombia: 167           |
| Country: Number of subjects enrolled | Mexico: 78              |
| Country: Number of subjects enrolled | Greece: 217             |
| Country: Number of subjects enrolled | Türkiye: 159            |
| Worldwide total number of subjects   | 6001                    |
| EEA total number of subjects         | 2768                    |

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)                      | 1262 |
| From 65 to 84 years                       | 4271 |
| 85 years and over                         | 468  |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at multiple centers in 37 countries/regions between 14-Sep-2020 (first participant first visit) and 14-Jun-2024 (last participant last visit).

### Pre-assignment

Screening details:

Of the 7463 screened participants, 1447 were screening failures, 6016 were randomized. Of the 3011 participants randomized into the finerenone group and the 3005 into the placebo group, 8 and 7 participants respectively were prospectively excluded from analysis due to major GCP violations.

### Period 1

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

### Arms

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

Arm description:

Participants received finerenone 10 mg, 20 mg or 40 mg once daily.

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Finerenone                 |
| Investigational medicinal product code | BAY94-8862                 |
| Other name                             | Kerendia, Firalta, Lyvelsa |
| Pharmaceutical forms                   | Film-coated tablet         |
| Routes of administration               | Oral use                   |

Dosage and administration details:

Oral tablet; For participants with an eGFR  $\leq 60$  mL/min/1.73 m<sup>2</sup>: Starting dose is 10 mg once daily (OD) and maximum dose 20 mg OD. For participants with an eGFR  $> 60$  mL/min/1.73 m<sup>2</sup>: Starting dose is 20 mg OD and maximum dose 40 mg OD. Dose could be up-titrated from Month 1 onwards or down-titrated at any time during the study. Study medication was administered 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:

Participants received matching placebo once daily.

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

Dosage and administration details:

Matching placebo, oral tablet, 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                               | 3003       | 2998    |
| Completed                             | 2996       | 2986    |
| Not completed                         | 7          | 12      |
| Consent withdrawn by subject          | 6          | 7       |
| Lost to follow-up                     | 1          | 5       |

## Baseline characteristics

### Reporting groups

|  |            |
|--|------------|
| Reporting group title  | Finerenone |
| Reporting group description:                                       |            |
| Participants received finerenone 10 mg, 20 mg or 40 mg once daily. |            |
| Reporting group title  | Placebo    |
| Reporting group description:                                       |            |
| Participants received matching placebo once daily.                 |            |

| Reporting group values  | Finerenone | Placebo | Total |
|---|------------|---------|-------|
| Number of subjects  | 3003       | 2998    | 6001  |
| Age categorical   |            |         |       |
| Units: Subjects   |            |         |       |
| Adults (18-64 years)  | 643        | 619     | 1262  |
| From 65-84 years  | 2134       | 2137    | 4271  |
| 85 years and over   | 226        | 242     | 468   |
| Age continuous  |            |         |       |
| Units: years  |            |         |       |
| arithmetic mean   | 71.94      | 72.04   |       |
| standard deviation  | ± 9.60     | ± 9.69  | -     |
| Gender categorical  |            |         |       |
| Units: Subjects   |            |         |       |
| Female  | 1355       | 1377    | 2732  |
| Male  | 1648       | 1621    | 3269  |
| NYHA class  |            |         |       |
| The New York Heart Association (NYHA) Functional Classification is a simple scale that classifies patients with heart failure based on the severity of their symptoms and how those symptoms affect their physical activity, which ranges from Class I to Class IV, a lower class number is indicative of a better condition. |            |         |       |
| Units: Subjects   |            |         |       |
| NYHA class II   | 2081       | 2065    | 4146  |
| NYHA class III  | 903        | 910     | 1813  |
| NYHA class IV   | 18         | 23      | 41    |
| missing   | 1          | 0       | 1     |
| Baseline LVEF   |            |         |       |
| LVEF: Left ventricular ejection fraction, which is used to assess how well the left ventricle of the heart pumps blood with each beat. A normal LVEF ranges from 55% to 70%. When the LVEF is below 55%, it suggests that the heart's pumping ability is reduced.   |            |         |       |
| Units: percent  |            |         |       |
| arithmetic mean   | 52.64      | 52.49   |       |
| standard deviation  | ± 7.82     | ± 7.81  | -     |

## End points

### End points reporting groups

|  |            |
|--|------------|
| Reporting group title  | Finerenone |
| Reporting group description:                                       |            |
| Participants received finerenone 10 mg, 20 mg or 40 mg once daily. |            |
| Reporting group title  | Placebo    |
| Reporting group description:                                       |            |
| Participants received matching placebo once daily.                 |            |

### Primary: Occurrence of the composite endpoint of cardiovascular death and total (first and recurrent) heart failure events

|  |   |
|--|---|
| End point title  | Occurrence of the composite endpoint of cardiovascular death and total (first and recurrent) heart failure events |
| End point description:   |   |
| Number of composite endpoint events of cardiovascular death and total (first and recurrent) heart failure (HF) events (hospitalization for heart failure or urgent HF visit) in HF patients. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| From randomization up until the end of study, with an average study duration of 32 months  |   |

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3003            | 2998            |  |  |
| Units: events               | 1083            | 1283            |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title              | Rate Ratio                     |
| Comparison groups                       | Finerenone v Placebo           |
| Number of subjects included in analysis | 6001                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[1]</sup>     |
| P-value                                 | = 0.0072 <sup>[2]</sup>        |
| Method                                  | stratified Andersen-Gill model |
| Parameter estimate                      | Rate ratio                     |
| Point estimate                          | 0.84                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.74                           |
| upper limit                             | 0.95                           |

Notes:

[1] - Stratified Andersen-Gill model with robust sandwich estimate for the covariance matrix of recurrent events

[2] - Two-sided p-value; p-value threshold=0.04967

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**Primary: Occurrence of the Composite Endpoint of Cardiovascular Death and Total (First and Recurrent) Heart Failure Events**

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|                 |  |
|-----------------|--|
| End point title | Occurrence of the Composite Endpoint of Cardiovascular Death and Total (First and Recurrent) Heart Failure Events <sup>[3]</sup> |
|-----------------|--|

End point description:

Number of participants with composite endpoint events of cardiovascular death and total (first and recurrent) heart failure (HF) events (hospitalization for heart failure or urgent HF visit) in HF patients.

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

End point timeframe:

From randomization up until the end of study, with an average study duration of 32 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This primary endpoint shares identical statistical analysis with the previous one.

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3003            | 2998            |  |  |
| Units: participants         | 624             | 719             |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Occurrence of total (first and recurrent) heart failure events**

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|                 |  |
|-----------------|--|
| End point title | Occurrence of total (first and recurrent) heart failure events |
|-----------------|--|

End point description:

Number of total (first and recurrent) heart failure events.

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

End point timeframe:

From randomization up until the end of study, with an average study duration of 32 months

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3003            | 2998            |  |  |
| Units: events               | 842             | 1024            |  |  |

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**Statistical analyses**

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|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Rate Ratio                     |
| Comparison groups                       | Placebo v Finerenone           |
| Number of subjects included in analysis | 6001                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[4]</sup>     |
| P-value                                 | = 0.0062 <sup>[5]</sup>        |
| Method                                  | Stratified Andersen-Gill model |
| Parameter estimate                      | Rate ratio                     |
| Point estimate                          | 0.82                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.71                           |
| upper limit                             | 0.94                           |

Notes:

[4] - Stratified Andersen-Gill model with robust sandwich estimate for the covariance matrix of recurrent events

[5] - Two-sided p-value; p-value threshold=0.04967

### Secondary: Occurrence of total (first and recurrent) heart failure events

|   |  |
|---|--|
| End point title   | Occurrence of total (first and recurrent) heart failure events |
| End point description:  |  |
| Number of participants with total (first and recurrent) heart failure events.             |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From randomization up until the end of study, with an average study duration of 32 months |  |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Finerenone      | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3003            | 2998            |  |  |
| Units: participants         | 479             | 573             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ)

|  |  |
|--|--|
| End point title  | Change from baseline in Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) |
| End point description:   |  |
| The Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) is ranged from 0 to 100. A higher score (closer to 100) reflects fewer symptoms, indicating better heart failure symptom status. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From baseline to Month 6, 9 and 12   |  |

| <b>End point values</b>                      | Finerenone          | Placebo             |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                  | 2731                | 2710                |  |  |
| Units: score on scale                        |                     |                     |  |  |
| least squares mean (confidence interval 95%) | 7.99 (7.37 to 8.62) | 6.43 (5.79 to 7.07) |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Difference in LS Mean   |
|---|-------------------------|
| Comparison groups                       | Finerenone v Placebo    |
| Number of subjects included in analysis | 5441                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[6]</sup>    |
| P-value                                 | < 0.0001 <sup>[7]</sup> |
| Method                                  | Mixed Models Analysis   |
| Parameter estimate                      | Difference in LS Mean   |
| Point estimate                          | 1.56                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.79                    |
| upper limit                             | 2.34                    |

Notes:

[6] - mixed-effects model for repeated measures (MMRM)

[7] - Two-sided p-value

## Secondary: Proportion of participants who showed improvement in NYHA class

| <b>End point title</b>  | Proportion of participants who showed improvement in NYHA class |
|---|---|
| End point description:  |   |
| The New York Heart Association (NYHA) Functional Classification is a simple scale that classifies patients with heart failure based on the severity of their symptoms and how those symptoms affect their physical activity, which ranges from Class I to Class IV, a lower class number is indicative of a better condition. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| from baseline to Month 12   |   |

| End point values                 | Finerenone             | Placebo                |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 3003                   | 2998                   |  |  |
| Units: Estimated proportion      |                        |                        |  |  |
| number (confidence interval 95%) | 0.179 (0.163 to 0.195) | 0.178 (0.162 to 0.194) |  |  |

## Statistical analyses

| Statistical analysis title              | Odds ratio Finerenone / Placebo |
|---|---------------------------------|
| Comparison groups                       | Finerenone v Placebo            |
| Number of subjects included in analysis | 6001                            |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other <sup>[8]</sup>            |
| P-value                                 | = 0.9295 <sup>[9]</sup>         |
| Method                                  | Regression, Logistic            |
| Parameter estimate                      | Odds ratio (OR)                 |
| Point estimate                          | 1.01                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.88                            |
| upper limit                             | 1.15                            |

Notes:

[8] - Logistic regression analysis

[9] - Two-sided p-value

## Secondary: First occurrence of renal composite events

|   |  |
|---|--|
| End point title   | First occurrence of renal composite events |
| End point description:  |  |
| Number of participants with renal composite events encompassing the components sustained decrease in eGFR $\geq 50\%$ relative to baseline over at least 4 weeks, sustained eGFR decline to $<15$ mL/min/1.73 m <sup>2</sup> over at least 4 weeks, initiation of chronic dialysis and renal transplantation. |  |
| End point type  | Secondary                                  |
| End point timeframe:  |  |
| From randomization up to end of study visit, with an average study duration of 32 months  |  |

| End point values            | Finerenone      | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 3003            | 2998            |  |  |
| Units: participants         | 75              | 55              |  |  |

## Statistical analyses

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Cause-specific Hazard Ratio |
| Comparison groups                       | Finerenone v Placebo        |
| Number of subjects included in analysis | 6001                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[10]</sup>       |
| P-value                                 | = 0.1071 <sup>[11]</sup>    |
| Method                                  | Stratified log-rank test    |
| Parameter estimate                      | Cause-specific Hazard Ratio |
| Point estimate                          | 1.33                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.94                        |
| upper limit                             | 1.89                        |

Notes:

[10] - Stratified Cox proportion hazards model

[11] - two-sided p-value

### Secondary: Occurrence of all-cause mortality (Full Analysis Set)

|  |   |
|--|---|
| End point title  | Occurrence of all-cause mortality (Full Analysis Set) |
| End point description:   |   |
| Number of participants with death due to any cause were reported as descriptive result. Number of participants with outcome death reported here includes deaths occurred after randomization until the end of the study visit. Deaths after end of study visit are not included in this table. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From randomization until end of 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 | 3003            | 2998            |  |  |
| Units: participants         | 491             | 522             |  |  |

### Statistical analyses

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Hazard Ratio                |
| Comparison groups                       | Finerenone v Placebo        |
| Number of subjects included in analysis | 6001                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[12]</sup>       |
| P-value                                 | = 0.2794 <sup>[13]</sup>    |
| Method                                  | Stratified log-rank         |
| Parameter estimate                      | Cause-specific hazard ratio |
| Point estimate                          | 0.93                        |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.83    |
| upper limit         | 1.06    |

Notes:

[12] - Stratified Cox proportion hazards model

[13] - Two-sided p-value

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) are considered from the start of study intervention up to 3 days after the last study intervention administration, with an average treatment duration of 28 months.

Adverse event reporting additional description:

The safety analysis set (SAF) included FAS participants who took  $\geq 1$  dose of study drug. 10 finerenone (n=3003) and 5 placebo participants (n=2998) took no drug, leaving 2993 in each SAF group. Heart failure and renal events were not counted as adverse events. All-cause mortality for FAS includes deaths from randomization to study end.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 27.0   |

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Finerenone (BAY94-8862) |
|-----------------------|-------------------------|

Reporting group description:

Participants randomized to this group with an eGFR  $\leq 60$  mL/min/1.73 m<sup>2</sup>: Starting dose is 10 mg once daily (OD) and maximum dose 20 mg OD. For participants with an eGFR  $> 60$  mL/min/1.73 m<sup>2</sup>: Starting dose is 20 mg OD and maximum dose 40 mg OD.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Never received treatment |
|-----------------------|--------------------------|

Reporting group description:

Participants were randomized to either Finerenone or Placebo but never received study intervention.

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

Reporting group description:

Participants randomized to this group received matching placebo once daily.

| Serious adverse events  | Finerenone (BAY94-8862) | Never received treatment | Placebo              |
|---|-------------------------|--------------------------|----------------------|
| Total subjects affected by serious adverse events                   |                         |                          |                      |
| subjects affected / exposed   | 1157 / 2993 (38.66%)    | 0 / 15 (0.00%)           | 1213 / 2993 (40.53%) |
| number of deaths (all causes)                                       | 494                     | 3                        | 528                  |
| number of deaths resulting from adverse events                      | 204                     | 0                        | 239                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                          |                      |
| Acute myeloid leukaemia   |                         |                          |                      |
| subjects affected / exposed   | 0 / 2993 (0.00%)        | 0 / 15 (0.00%)           | 1 / 2993 (0.03%)     |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 0                    | 0 / 1                |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    | 0 / 1                |
| Adenocarcinoma  |                         |                          |                      |
| subjects affected / exposed   | 0 / 2993 (0.00%)        | 0 / 15 (0.00%)           | 1 / 2993 (0.03%)     |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 0                    | 0 / 1                |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    | 0 / 0                |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| Adenocarcinoma gastric                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Adenocarcinoma of colon                         |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Adenoma benign                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| B-cell small lymphocytic lymphoma               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Basal cell carcinoma                            |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Benign neoplasm of adrenal gland                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Benign neoplasm of skin                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bile duct cancer                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Bladder cancer                                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bladder neoplasm                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bone neoplasm                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bowen's disease                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Breast cancer                                   |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Breast cancer recurrent                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Breast cancer stage II                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Breast neoplasm                                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Carcinoma in situ of penis                      |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholangiocarcinoma                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 0            |
| Chronic lymphocytic leukaemia                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colon cancer                                    |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diffuse large B-cell lymphoma                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Endometrial cancer                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastric cancer                                  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1            |
| Gastrointestinal carcinoma                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemangioma                                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hodgkin's disease                               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Laryngeal neoplasm                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Lipoma  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lung adenocarcinoma                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lymphoma  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Malignant melanoma                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mediastinum neoplasm                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Mesothelioma                                    |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Metastases to bone                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Metastases to liver                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Metastases to lymph nodes                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Metastases to spine                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Neoplasm  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Neoplasm skin                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal adenocarcinoma                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 2            |
| Ovarian cancer                                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatic carcinoma                            |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 1            |
| Papillary serous endometrial carcinoma          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Papillary thyroid cancer                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Plasma cell myeloma                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostate cancer metastatic                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostate cancer recurrent                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostate cancer stage I                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostatic adenoma                               |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rectal cancer                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal cancer                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Sarcoma uterus                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Small cell lung cancer                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Squamous cell carcinoma                         |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Squamous cell carcinoma of skin                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Squamous cell carcinoma of the oral cavity      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Squamous cell carcinoma of the tongue           |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tongue neoplasm malignant stage unspecified     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Tonsil cancer                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Transitional cell carcinoma                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ureteric cancer                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tumour ulceration                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Metastases to salivary gland                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Breast cancer metastatic                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Colon cancer metastatic                         |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Retroperitoneal neoplasm                        |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Lung neoplasm malignant                         |                   |                |                   |
| subjects affected / exposed                     | 8 / 2993 (0.27%)  | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 0          | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 0          | 0 / 2             |
| Metastases to central nervous system            |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Gastric adenoma                                 |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Prostate cancer                                 |                   |                |                   |
| subjects affected / exposed                     | 11 / 2993 (0.37%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 0          | 0 / 9             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Brain neoplasm                                  |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Colon neoplasm                                  |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Malignant mediastinal neoplasm                  |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Paraganglion neoplasm                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colorectal cancer                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal neoplasm                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal squamous cell carcinoma             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Adrenal neoplasm                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatic neoplasm                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Salivary gland cancer                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lip neoplasm                                    |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lung infiltration malignant                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lung neoplasm                                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rosai-Dorfman syndrome                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Metastatic squamous cell carcinoma              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Thyroid cancer                                  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ovarian cancer recurrent                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Laryngeal cancer metastatic                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic cancer                                  |                  |                |                  |

|  |                  |                |                  |
|--|------------------|----------------|------------------|
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 1            |
| Hepatocellular carcinoma                             |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Invasive ductal breast carcinoma                     |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Ovarian granulosa cell tumour                        |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Anal squamous cell carcinoma                         |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Intraductal papillary-mucinous carcinoma of pancreas |                  |                |                  |
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Small intestine adenocarcinoma                       |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 1            |
| Myeloproliferative neoplasm                          |                  |                |                  |
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Neuroendocrine tumour of the lung                    |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Follicular lymphoma stage II                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Malignant gastric ulcer                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colorectal adenoma                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vascular disorders                              |                  |                |                  |
| Accelerated hypertension                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Aortic aneurysm                                 |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Aortic dissection                               |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 0            |
| Aortic stenosis                                 |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Arterial thrombosis                             |                  |                |                  |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Blood pressure fluctuation                      |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Circulatory collapse                            |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Embolism arterial                               |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Essential hypertension                          |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Femoral artery aneurysm                         |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Haematoma                                       |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Hypertension                                    |                  |                |                   |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Hypertensive crisis                             |                  |                |                   |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypotension                                     |                   |                |                  |
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 8 / 14            | 0 / 0          | 1 / 9            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypovolaemic shock                              |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Intermittent claudication                       |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Lymphoedema                                     |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Orthostatic hypotension                         |                   |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 1 / 4             | 0 / 0          | 2 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Peripheral ischaemia                            |                   |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Peripheral vascular disorder                    |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Thrombosis                                      |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Varicose ulceration                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Varicose vein                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Labile hypertension                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shock haemorrhagic                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Dry gangrene                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Deep vein thrombosis                            |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemorrhage                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peripheral artery occlusion                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypertensive emergency                          |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypertensive urgency                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Extremity necrosis                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Arterial haemorrhage                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Embolism  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peripheral embolism                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diabetic vascular disorder                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peripheral arterial occlusive disease           |                  |                |                  |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 10 / 2993 (0.33%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 0          | 0 / 12           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Aortic arteriosclerosis                         |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Aortic dissection rupture                       |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1            |
| Subgaleal haematoma                             |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Peripheral artery stenosis                      |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Peripheral artery thrombosis                    |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Obstructive shock                               |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Peripheral venous disease                       |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Brachiocephalic arteriosclerosis                |                   |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Brachiocephalic artery stenosis                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Surgical and medical procedures                 |                  |                |                  |
| Angioplasty                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Aortic valve replacement                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Appendectomy                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bladder calculus removal                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac pacemaker insertion                     |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac pacemaker removal                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardioversion                                   |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Carotid endarterectomy                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholecystectomy                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cryotherapy                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Glossectomy                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hip arthroplasty                                |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Inguinal hernia repair                          |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Knee arthroplasty                               |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Leg amputation                                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pelvic floor repair                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal stone removal                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal laminectomy                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Toe amputation                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Transurethral prostatectomy                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Umbilical hernia repair                         |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ureteric calculus removal                       |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Urethrotomy                                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac pacemaker replacement                   |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Implantable defibrillator insertion             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Knee operation                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shoulder arthroplasty                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Coronary angioplasty                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hip surgery                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Coronary arterial stent insertion               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholelithotomy                                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Polypectomy                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rehabilitation therapy                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal artery angioplasty                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peripheral artery angioplasty                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peripheral nerve decompression                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac resynchronisation therapy               |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac ablation                                |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haematoma evacuation                            |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac operation                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colectomy                                       |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostatectomy                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastrectomy                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Retinal operation                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shoulder operation                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Percutaneous coronary intervention              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intraocular lens implant                        |                  |                |                  |

|  |                  |                |                  |
|--|------------------|----------------|------------------|
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Eventration repair                                   |                  |                |                  |
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Urinary incontinence surgery                         |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Transcatheter aortic valve implantation              |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Metabolic surgery                                    |                  |                |                  |
| subjects affected / exposed                          | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Atrial appendage closure                             |                  |                |                  |
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| Drug titration                                       |                  |                |                  |
| subjects affected / exposed                          | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 0            |
| General disorders and administration site conditions |                  |                |                  |
| Asthenia   |                  |                |                  |
| subjects affected / exposed                          | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all      | 1 / 6            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          | 0 / 1            |
| Chest discomfort                                     |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Chest pain                                      |                   |                |                   |
| subjects affected / exposed                     | 23 / 2993 (0.77%) | 0 / 15 (0.00%) | 22 / 2993 (0.74%) |
| occurrences causally related to treatment / all | 0 / 31            | 0 / 0          | 0 / 23            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Condition aggravated                            |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Death   |                   |                |                   |
| subjects affected / exposed                     | 29 / 2993 (0.97%) | 0 / 15 (0.00%) | 52 / 2993 (1.74%) |
| occurrences causally related to treatment / all | 0 / 29            | 0 / 0          | 0 / 52            |
| deaths causally related to treatment / all      | 0 / 29            | 0 / 0          | 0 / 52            |
| Fatigue   |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Gait disturbance                                |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Hernia  |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Hyperpyrexia                                    |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Hypothermia                                     |                   |                |                   |



|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Impaired healing                                |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Incarcerated hernia                             |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Malaise   |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Oedema peripheral                               |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Pyrexia   |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 8 / 2993 (0.27%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 8             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Sudden death                                    |                   |                |                   |
| subjects affected / exposed                     | 16 / 2993 (0.53%) | 0 / 15 (0.00%) | 17 / 2993 (0.57%) |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 0          | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 16            | 0 / 0          | 0 / 17            |
| Sudden cardiac death                            |                   |                |                   |
| subjects affected / exposed                     | 14 / 2993 (0.47%) | 0 / 15 (0.00%) | 16 / 2993 (0.53%) |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 0          | 0 / 16            |
| deaths causally related to treatment / all      | 0 / 14            | 0 / 0          | 0 / 16            |
| General physical health deterioration           |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pacemaker generated arrhythmia                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Inflammation                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Polyp   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Non-cardiac chest pain                          |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prosthetic cardiac valve thrombosis             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Accidental death                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1            |
| Medical device site haematoma                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vascular stent stenosis                         |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Multiple organ dysfunction syndrome             |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 1            |
| Immune system disorders                         |                  |                |                  |
| Amyloidosis                                     |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Anaphylactic shock                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Anaphylactoid reaction                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Primary amyloidosis                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Sarcoidosis                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Social circumstances                            |                  |                |                  |
| Immobile  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Reproductive system and breast                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| disorders                                       |                  |                |                  |
| Benign prostatic hyperplasia                    |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Breast mass                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cystocele                                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Endometrial hyperplasia                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intermenstrual bleeding                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Scrotal swelling                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Uterine polyp                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Postmenopausal haemorrhage                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ovarian haemorrhage                             |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Respiratory, thoracic and mediastinal disorders |                   |                |                   |
| Acute pulmonary oedema                          |                   |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Acute respiratory failure                       |                   |                |                   |
| subjects affected / exposed                     | 10 / 2993 (0.33%) | 0 / 15 (0.00%) | 17 / 2993 (0.57%) |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 0          | 0 / 18            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0          | 0 / 2             |
| Asphyxia  |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Asthma  |                   |                |                   |
| subjects affected / exposed                     | 8 / 2993 (0.27%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atelectasis                                     |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Bronchitis chronic                              |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Bronchospasm                                    |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Chronic obstructive pulmonary disease           |                   |                |                   |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 18 / 2993 (0.60%) | 0 / 15 (0.00%) | 27 / 2993 (0.90%) |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 0          | 0 / 32            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Chronic respiratory failure                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Cough   |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Dyspnoea  |                   |                |                   |
| subjects affected / exposed                     | 14 / 2993 (0.47%) | 0 / 15 (0.00%) | 13 / 2993 (0.43%) |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 0          | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 1             |
| Dyspnoea exertional                             |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Emphysema                                       |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Epistaxis                                       |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Haemoptysis                                     |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Haemothorax                                     |                   |                |                   |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Hypoxia   |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Interstitial lung disease                       |                  |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%)  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 3             |
| Laryngeal stenosis                              |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1             |
| Lung disorder                                   |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Malignant pleural effusion                      |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Pickwickian syndrome                            |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Pleural effusion                                |                  |                |                   |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0          | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0             |
| Pleurisy  |                  |                |                   |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pneumonitis                                     |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pneumonitis aspiration                          |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pneumothorax                                    |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pneumothorax spontaneous                        |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pulmonary alveolar haemorrhage                  |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pulmonary congestion                            |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pulmonary embolism                              |                   |                |                  |
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0          | 0 / 0            |
| Pulmonary fibrosis                              |                   |                |                  |



|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pulmonary hypertension                          |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Pulmonary oedema                                |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 2            |
| Respiratory acidosis                            |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Respiratory alkalosis                           |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Respiratory arrest                              |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0            |
| Respiratory distress                            |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Respiratory failure                             |                   |                |                  |
| subjects affected / exposed                     | 11 / 2993 (0.37%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 0          | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 1            |
| Sleep apnoea syndrome                           |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hydrothorax                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tracheal stenosis                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pulmonary mass                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Acquired diaphragmatic eventration              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Obstructive airways disorder                    |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bronchial wall thickening                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oropharyngeal pain                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Psychiatric disorders                           |                  |                |                  |
| Agitation                                       |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Completed suicide                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Confusional state                               |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Conversion disorder                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Delirium  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Depression                                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Disorientation                                  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Eating disorder                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hallucination                                   |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mania   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Panic attack                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Sleep disorder                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mental status changes                           |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Suicidal behaviour                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Somatic symptom disorder                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mixed anxiety and depressive disorder           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Product issues                                  |                  |                |                  |
| Device malfunction                              |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Device dislocation                              |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Device fastener issue                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Device inappropriate shock delivery             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Device loosening                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatobiliary disorders                         |                  |                |                  |
| Acute hepatic failure                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Alcoholic liver disease                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Autoimmune hepatitis                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bile duct stone                                 |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Biliary colic                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholangitis                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholangitis acute                               |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholecystitis                                   |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholecystitis acute                             |                  |                |                  |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Cholecystitis chronic                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cholelithiasis                                  |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cirrhosis alcoholic                             |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic cirrhosis                               |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic failure                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic function abnormal                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatitis alcoholic                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Jaundice cholestatic                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Non-alcoholic steatohepatitis                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Biliary dyskinesia                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hydrocholecystis                                |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic lesion                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Congestive hepatopathy                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Investigations                                  |                  |                |                  |
| Biopsy prostate                                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Blood creatine phosphokinase MB increased       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Blood potassium increased                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Blood sodium decreased                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Carcinoembryonic antigen increased              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Glomerular filtration rate decreased            |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemoglobin decreased                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Heart rate decreased                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intraocular pressure decreased                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ureteroscopy                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Weight decreased                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Weight increased                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| White blood cell count increased                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ejection fraction decreased                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Anticoagulation drug level above therapeutic    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal function test abnormal                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Occult blood positive                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Angiocardiogram                                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| SARS-CoV-2 test positive                        |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Computerised tomogram heart abnormal            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Injury, poisoning and procedural complications  |                  |                |                  |
| Accident  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |

|   |                  |                |                  |  |
|---|------------------|----------------|------------------|--|
| Alcohol poisoning                               |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Ankle fracture                                  |                  |                |                  |  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Burns second degree                             |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Carbon monoxide poisoning                       |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |  |
| Clavicle fracture                               |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Compression fracture                            |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Concussion                                      |                  |                |                  |  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Extradural haematoma                            |                  |                |                  |  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |  |
| Fall  |                  |                |                  |  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 15 / 2993 (0.50%) | 0 / 15 (0.00%) | 14 / 2993 (0.47%) |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 0          | 0 / 14            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Femoral neck fracture                           |                   |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 9 / 2993 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 9             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Femur fracture                                  |                   |                |                   |
| subjects affected / exposed                     | 15 / 2993 (0.50%) | 0 / 15 (0.00%) | 17 / 2993 (0.57%) |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 0          | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Foot fracture                                   |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Forearm fracture                                |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Fractured sacrum                                |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Head injury                                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Heat stroke                                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Hip fracture                                    |                   |                |                   |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Humerus fracture                                |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hyphaema  |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Incisional hernia                               |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Jaw fracture                                    |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Multiple fractures                              |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Multiple injuries                               |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Muscle rupture                                  |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Overdose  |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Patella fracture                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pulmonary contusion                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Radius fracture                                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rib fracture                                    |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Road traffic accident                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Snake bite                                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal compression fracture                     |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal cord injury cervical                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal fracture                                 |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Subcutaneous haematoma                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Subdural haematoma                              |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0          | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0          | 0 / 2            |
| Synovial rupture                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tibia fracture                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Wrist fracture                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vascular pseudoaneurysm                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shoulder fracture                               |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cervical vertebral fracture                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lumbar vertebral fracture                       |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Thoracic vertebral fracture                     |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Face injury                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Contusion                                       |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Post procedural haemorrhage                     |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Traumatic haemorrhage                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Thermal burn                                    |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Skin laceration                                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shunt stenosis                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Incision site haematoma                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Postpericardiotomy syndrome                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pelvic fracture                                 |                  |                |                  |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Limb injury                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Traumatic intracranial haemorrhage              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Upper limb fracture                             |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lower limb fracture                             |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Post procedural haematoma                       |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Shunt aneurysm                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Procedural pain                                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Skin abrasion                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal column injury                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Toxicity to various agents                      |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Craniocerebral injury                           |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Meniscus injury                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Eye contusion                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Traumatic haemothorax                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Adjacent segment degeneration                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Craniofacial fracture                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Nasal injury                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Injury of conjunctiva                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Congenital, familial and genetic disorders      |                  |                |                  |
| Dermoid cyst                                    |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Familial amyloidosis                            |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Hydrocele                                       |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Janus kinase 2 mutation                         |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardiac disorders                               |                   |                |                   |
| Acute myocardial infarction                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Angina pectoris                                 |                   |                |                   |
| subjects affected / exposed                     | 17 / 2993 (0.57%) | 0 / 15 (0.00%) | 26 / 2993 (0.87%) |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 0          | 0 / 30            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Angina unstable                                 |                   |                |                   |
| subjects affected / exposed                     | 38 / 2993 (1.27%) | 0 / 15 (0.00%) | 36 / 2993 (1.20%) |
| occurrences causally related to treatment / all | 0 / 43            | 0 / 0          | 0 / 38            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Aortic valve incompetence                       |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Aortic valve stenosis                           |                   |                |                   |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Arrhythmia                                      |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Arrhythmia supraventricular                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Arteriosclerosis coronary artery                |                   |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 5 / 2993 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Atrial fibrillation                             |                   |                |                   |
| subjects affected / exposed                     | 77 / 2993 (2.57%) | 0 / 15 (0.00%) | 73 / 2993 (2.44%) |
| occurrences causally related to treatment / all | 1 / 95            | 0 / 0          | 0 / 101           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atrial flutter                                  |                   |                |                   |
| subjects affected / exposed                     | 14 / 2993 (0.47%) | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atrial tachycardia                              |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atrioventricular block                          |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atrioventricular block complete                 |                   |                |                   |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 6 / 2993 (0.20%)  | 0 / 15 (0.00%) | 5 / 2993 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 0          | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Atrioventricular block second degree            |                   |                |                   |
| subjects affected / exposed                     | 5 / 2993 (0.17%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Bradycardia                                     |                   |                |                   |
| subjects affected / exposed                     | 7 / 2993 (0.23%)  | 0 / 15 (0.00%) | 9 / 2993 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardiac amyloidosis                             |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Cardiac aneurysm                                |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardiac arrest                                  |                   |                |                   |
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 0          | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 0          | 0 / 10            |
| Cardiac failure                                 |                   |                |                   |
| subjects affected / exposed                     | 18 / 2993 (0.60%) | 0 / 15 (0.00%) | 18 / 2993 (0.60%) |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 0          | 2 / 20            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 7             |
| Cardiac failure acute                           |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Cardiac failure congestive                      |                   |                |                   |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardiac tamponade                               |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardio-respiratory arrest                       |                   |                |                   |
| subjects affected / exposed                     | 5 / 2993 (0.17%)  | 0 / 15 (0.00%) | 6 / 2993 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0          | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 0          | 0 / 6             |
| Cardiogenic shock                               |                   |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 2             |
| Cardiovascular disorder                         |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Conduction disorder                             |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cor pulmonale                                   |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Coronary artery disease                         |                   |                |                   |
| subjects affected / exposed                     | 20 / 2993 (0.67%) | 0 / 15 (0.00%) | 17 / 2993 (0.57%) |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 0          | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0          | 0 / 1             |
| Coronary artery occlusion                       |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Coronary artery stenosis                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Left ventricular failure                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mitral valve incompetence                       |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Myocardial fibrosis                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Myocardial infarction                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Myocardial ischaemia                            |                  |                |                  |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0          | 0 / 3            |
| Palpitations                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pericardial effusion                            |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pericarditis                                    |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pericarditis constrictive                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Sinoatrial block                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Sinus bradycardia                               |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Supraventricular extrasystoles                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Supraventricular tachycardia                    |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tachycardia                                     |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tachycardia paroxysmal                          |                  |                |                  |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Tricuspid valve incompetence                    |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Ventricular arrhythmia                          |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1             |
| Ventricular extrasystoles                       |                  |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Ventricular fibrillation                        |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0             |
| Ventricular tachycardia                         |                  |                |                   |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 13 / 2993 (0.43%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0          | 0 / 18            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Atrial thrombosis                               |                  |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Cardiac pseudoaneurysm                          |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Bradyarrhythmia                                 |                  |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiovascular deconditioning                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiopulmonary failure                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 3            |
| Acute coronary syndrome                         |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diastolic dysfunction                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Dilated cardiomyopathy                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tricuspid valve disease                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cardiac valve disease                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Mitral valve disease                            |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Ventricular tachyarrhythmia                     |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Stress cardiomyopathy                           |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cardiorenal syndrome                            |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Microvascular coronary artery disease           |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Sinus node dysfunction                          |                   |                |                   |
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Chronic coronary syndrome                       |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Nervous system disorders                        |                   |                |                   |
| Aphasia   |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Ataxia  |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bell's palsy                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Carotid artery stenosis                         |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Carpal tunnel syndrome                          |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cerebral artery occlusion                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cerebral haemorrhage                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Cerebral infarction                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cerebral ischaemia                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Cervicobrachial syndrome                        |                  |                |                  |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Dementia  |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0            |
| Dementia Alzheimer's type                       |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Diabetic neuropathy                             |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Dizziness                                       |                   |                |                  |
| subjects affected / exposed                     | 12 / 2993 (0.40%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 3 / 12            | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Drop attacks                                    |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Dysarthria                                      |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Encephalopathy                                  |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1            |
| Epilepsy  |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Guillain-Barre syndrome                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Headache  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hepatic encephalopathy                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hydrocephalus                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypertensive encephalopathy                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intraventricular haemorrhage                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Loss of consciousness                           |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Movement disorder                               |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Myelopathy                                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Neuralgia                                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Paraesthesia                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Paralysis                                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Parkinsonism                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Polyneuropathy                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Post herpetic neuralgia                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Presyncope                                      |                  |                |                  |



|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Quadriplegia                                    |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Radiculopathy                                   |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Sciatica  |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Seizure   |                   |                |                   |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Spondylitic myelopathy                          |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Subarachnoid haemorrhage                        |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 6 / 2993 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 2             |
| Syncope   |                   |                |                   |
| subjects affected / exposed                     | 25 / 2993 (0.84%) | 0 / 15 (0.00%) | 22 / 2993 (0.74%) |
| occurrences causally related to treatment / all | 2 / 26            | 0 / 0          | 1 / 23            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Toxic encephalopathy                            |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Transient ischaemic attack                      |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vertebrobasilar insufficiency                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Wernicke's encephalopathy                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Carotid artery occlusion                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Quadripareisis                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal epidural haematoma                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lumbar radiculopathy                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lacunar infarction                              |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cerebrovascular insufficiency                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ischaemic stroke                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Parkinson's disease                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Metabolic encephalopathy                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vascular encephalopathy                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Orthostatic intolerance                         |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Brain injury                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypoxic-ischaemic encephalopathy                |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Lumbosacral radiculopathy                       |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Post cardiac arrest syndrome                    |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Thoracic radiculopathy                          |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Alcoholic encephalopathy                        |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Blood and lymphatic system disorders            |                   |                |                   |
| Anaemia   |                   |                |                   |
| subjects affected / exposed                     | 34 / 2993 (1.14%) | 0 / 15 (0.00%) | 31 / 2993 (1.04%) |
| occurrences causally related to treatment / all | 2 / 42            | 0 / 0          | 0 / 36            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0          | 0 / 0             |
| Anaemia macrocytic                              |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Anaemia of chronic disease                      |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Anaemia vitamin B12 deficiency                  |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Disseminated intravascular coagulation          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Febrile neutropenia                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypochromic anaemia                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Iron deficiency anaemia                         |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 1 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Leukocytosis                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lymphadenopathy mediastinal                     |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Microcytic anaemia                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Neutropenia                                     |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Normocytic anaemia                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Splenic haematoma                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Thrombocytopenia                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Nephrogenic anaemia                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spontaneous haematoma                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Blood loss anaemia                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Immune thrombocytopenia                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ear and labyrinth disorders                     |                  |                |                  |
| Tinnitus  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vertigo   |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vertigo positional                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypoacusis                                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Eye disorders                                   |                  |                |                  |
| Cataract  |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 1 / 10           | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cataract subcapsular                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diabetic eye disease                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diplopia  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Dry eye   |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Glaucoma  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Macular degeneration                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Open angle glaucoma                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ophthalmoplegia                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Retinal detachment                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vitreous haemorrhage                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Age-related macular degeneration                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Neovascular age-related macular degeneration    |                  |                |                  |



|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Gastrointestinal disorders                      |                  |                |                   |
| Abdominal adhesions                             |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Abdominal discomfort                            |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Abdominal pain                                  |                  |                |                   |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Abdominal pain upper                            |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Acute abdomen                                   |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Anal fistula                                    |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Ascites   |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Chronic gastritis                               |                  |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colitis   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Colitis ischaemic                               |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Constipation                                    |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Dental caries                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diarrhoea                                       |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 1 / 8            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diverticulum                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diverticulum intestinal haemorrhagic            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Duodenal ulcer                                  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Duodenal ulcer haemorrhage                      |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Duodenitis                                      |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Dysphagia                                       |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Enteritis                                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Enterocolitis                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastric polyps                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastric ulcer                                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastric ulcer haemorrhage                       |                  |                |                  |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0            |
| Gastric ulcer perforation                       |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gastritis                                       |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gastritis erosive                               |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gastrointestinal fistula                        |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gastrooesophageal reflux disease                |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gastrointestinal haemorrhage                    |                   |                |                  |
| subjects affected / exposed                     | 17 / 2993 (0.57%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 0          | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0          | 0 / 0            |
| Gastrointestinal necrosis                       |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Haematemesis                                    |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haematochezia                                   |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemorrhoids                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemorrhoids thrombosed                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hiatus hernia                                   |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ileus   |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ileus paralytic                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Incarcerated inguinal hernia                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Inguinal hernia                                 |                  |                |                  |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 14 / 2993 (0.47%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 15            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Inguinal hernia, obstructive                    |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Intestinal ischaemia                            |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0          | 0 / 1             |
| Intestinal obstruction                          |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1             |
| Intestinal perforation                          |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1             |
| Irritable bowel syndrome                        |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Large intestine perforation                     |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Melaena   |                  |                |                   |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Nausea  |                  |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Obstruction gastric                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Obturator hernia                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oedema mouth                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal achalasia                           |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal obstruction                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal ulcer                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Oesophageal varices haemorrhage                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Oesophagitis                                    |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatic haemorrhage                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatitis                                    |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatitis acute                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Pancreatitis chronic                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Proctitis ulcerative                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rectal haemorrhage                              |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rectal ulcer haemorrhage                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Small intestinal obstruction                    |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Small intestinal perforation                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Thrombosis mesenteric vessel                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Tooth impacted                                  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Umbilical hernia                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Upper gastrointestinal haemorrhage              |                  |                |                  |
| subjects affected / exposed                     | 5 / 2993 (0.17%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Vomiting  |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pancreatic mass                                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Lower gastrointestinal haemorrhage              |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Enterocutaneous fistula                         |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Large intestine polyp                           |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Acquired oesophageal web                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haemorrhoidal haemorrhage                       |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Salivary gland mass                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hernial eventration                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intestinal haemorrhage                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Duodenogastric reflux                           |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Abdominal hernia obstructive                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Abdominal hernia                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intra-abdominal haemorrhage                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Erosive duodenitis                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastrooesophageal sphincter insufficiency       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastrointestinal inflammation                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Incarcerated umbilical hernia                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Bile acid malabsorption                         |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Large intestinal stenosis                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Abdominal incarcerated hernia                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Strangulated umbilical hernia                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Anal incontinence                               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Obstructive pancreatitis                        |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Skin and subcutaneous tissue disorders          |                  |                |                  |
| Decubitus ulcer                                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Dermatitis                                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Henoch-Schonlein purpura                        |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hypersensitivity vasculitis                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rash  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Skin erosion                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Skin ulcer                                      |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Toxic skin eruption                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diabetic foot                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal and urinary disorders                     |                  |                |                  |
| Anuria  |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Calculus bladder                                |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Cystitis haemorrhagic                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haematuria                                      |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Hydronephrosis                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intercapillary glomerulosclerosis               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Nephrolithiasis                                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Nephropathy                                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Nephrotic syndrome                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Polyuria  |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal artery stenosis                           |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal failure                                   |                  |                |                  |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 3 / 8            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Renal infarct                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Ureteric stenosis                               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Urinary incontinence                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Urinary retention                               |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Urinary tract disorder                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tubulointerstitial nephritis                    |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 1 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Postrenal failure                               |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Renal injury                                    |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Diabetic nephropathy                            |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Renal impairment                                |                   |                |                   |
| subjects affected / exposed                     | 10 / 2993 (0.33%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 5 / 10            | 0 / 0          | 5 / 11            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cystitis noninfective                           |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Chronic kidney disease                          |                   |                |                   |
| subjects affected / exposed                     | 7 / 2993 (0.23%)  | 0 / 15 (0.00%) | 6 / 2993 (0.20%)  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 0          | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Urethral stenosis                               |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Stress urinary incontinence                     |                   |                |                   |



|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Acute kidney injury                             |                   |                |                   |
| subjects affected / exposed                     | 54 / 2993 (1.80%) | 0 / 15 (0.00%) | 28 / 2993 (0.94%) |
| occurrences causally related to treatment / all | 16 / 56           | 0 / 0          | 5 / 30            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| Prerenal failure                                |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Ureterolithiasis                                |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Subcapsular renal haematoma                     |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Endocrine disorders                             |                   |                |                   |
| Cushing's syndrome                              |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Hyperthyroidism                                 |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Musculoskeletal and connective tissue disorders |                   |                |                   |
| Arthralgia                                      |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 7 / 2993 (0.23%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 7             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| Arthritis                                       |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Back pain                                       |                   |                |                  |
| subjects affected / exposed                     | 10 / 2993 (0.33%) | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 0          | 1 / 8            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Cervical spinal stenosis                        |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Haemarthrosis                                   |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Joint swelling                                  |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Lumbar spinal stenosis                          |                   |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Muscle haemorrhage                              |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Muscle spasms                                   |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Muscular weakness                               |                   |                |                  |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Musculoskeletal pain                            |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Myalgia   |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Osteitis  |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Osteoarthritis                                  |                  |                |                   |
| subjects affected / exposed                     | 9 / 2993 (0.30%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 0          | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Osteochondrosis                                 |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Osteonecrosis                                   |                  |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Osteoporosis                                    |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Pathological fracture                           |                  |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Polyarthritis                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rheumatoid arthritis                            |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rotator cuff syndrome                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Scleroderma                                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal osteoarthritis                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Synovial cyst                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tenosynovitis                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Mobility decreased                              |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Neck mass                                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intervertebral disc protrusion                  |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Musculoskeletal chest pain                      |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Haematoma muscle                                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Connective tissue inflammation                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Connective tissue disorder                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Foot deformity                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Intervertebral disc disorder                    |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spondylolisthesis                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal pain                                     |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Spinal stenosis                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Immobilisation syndrome                         |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Infections and infestations                     |                  |                |                  |
| Abdominal wall abscess                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Acute sinusitis                                 |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Appendicitis                                    |                  |                |                  |
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bacteraemia                                     |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 4 / 2993 (0.13%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Bronchitis                                      |                   |                |                   |
| subjects affected / exposed                     | 13 / 2993 (0.43%) | 0 / 15 (0.00%) | 11 / 2993 (0.37%) |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 0          | 0 / 15            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Bronchopulmonary aspergillosis allergic         |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Cellulitis                                      |                   |                |                   |
| subjects affected / exposed                     | 17 / 2993 (0.57%) | 0 / 15 (0.00%) | 24 / 2993 (0.80%) |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 0          | 0 / 25            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Dacryocystitis                                  |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Diverticulitis                                  |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Diverticulitis intestinal haemorrhagic          |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Encephalomyelitis                               |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Endocarditis                                    |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Endocarditis staphylococcal                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Epididymitis                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Erysipelas                                      |                  |                |                  |
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Escherichia sepsis                              |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Fournier's gangrene                             |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Gangrene  |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Gas gangrene                                    |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastroenteritis                                 |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Gastroenteritis salmonella                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastroenteritis viral                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Herpes zoster                                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Infected skin ulcer                             |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Influenza                                       |                  |                |                  |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Liver abscess                                   |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Localised infection                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Lower respiratory tract infection               |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 6 / 2993 (0.20%) | 0 / 15 (0.00%) | 7 / 2993 (0.23%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Nasopharyngitis                                 |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Osteomyelitis                                   |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 4 / 2993 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Osteomyelitis acute                             |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Osteomyelitis chronic                           |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pelvic inflammatory disease                     |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Periodontitis                                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Peritonitis                                     |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1            |
| Peritonsillar abscess                           |                  |                |                  |

|   |                   |                |                    |
|---|-------------------|----------------|--------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia                                       |                   |                |                    |
| subjects affected / exposed                     | 87 / 2993 (2.91%) | 0 / 15 (0.00%) | 110 / 2993 (3.68%) |
| occurrences causally related to treatment / all | 0 / 98            | 0 / 0          | 0 / 116            |
| deaths causally related to treatment / all      | 0 / 15            | 0 / 0          | 0 / 13             |
| Pneumonia aspiration                            |                   |                |                    |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 5 / 2993 (0.17%)   |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 5              |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 2              |
| Pneumonia influenzal                            |                   |                |                    |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia legionella                            |                   |                |                    |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia moraxella                             |                   |                |                    |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia pseudomonal                           |                   |                |                    |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)   |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia respiratory syncytial viral           |                   |                |                    |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0              |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0              |
| Pneumonia viral                                 |                   |                |                    |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Postoperative wound infection                   |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Prostatic abscess                               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pulmonary tuberculosis                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pyelonephritis                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pyelonephritis acute                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pyoderma  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pyonephrosis                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Salmonellosis                                   |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Sepsis  |                   |                |                   |
| subjects affected / exposed                     | 25 / 2993 (0.84%) | 0 / 15 (0.00%) | 16 / 2993 (0.53%) |
| occurrences causally related to treatment / all | 0 / 25            | 0 / 0          | 1 / 16            |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 0          | 0 / 3             |
| Septic arthritis staphylococcal                 |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1             |
| Septic shock                                    |                   |                |                   |
| subjects affected / exposed                     | 7 / 2993 (0.23%)  | 0 / 15 (0.00%) | 9 / 2993 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 0          | 0 / 9             |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0          | 0 / 2             |
| Skin infection                                  |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Subacute endocarditis                           |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Subcutaneous abscess                            |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Tooth abscess                                   |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Tracheobronchitis                               |                   |                |                   |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Tuberculosis of intrathoracic lymph nodes       |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Tuberculous pleurisy                            |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Upper respiratory tract infection               |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 4 / 2993 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0          | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Urinary tract infection                         |                   |                |                   |
| subjects affected / exposed                     | 29 / 2993 (0.97%) | 0 / 15 (0.00%) | 26 / 2993 (0.87%) |
| occurrences causally related to treatment / all | 0 / 31            | 0 / 0          | 0 / 28            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 2             |
| Urinary tract infection enterococcal            |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Wound infection                                 |                   |                |                   |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Urosepsis                                       |                   |                |                   |
| subjects affected / exposed                     | 5 / 2993 (0.17%)  | 0 / 15 (0.00%) | 5 / 2993 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0          | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0          | 0 / 0             |
| Bursitis infective staphylococcal               |                   |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Anal abscess                                    |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Streptococcal sepsis                            |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Neutropenic sepsis                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Abscess limb                                    |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Staphylococcal bacteraemia                      |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pulmonary sepsis                                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 2            |
| Coronavirus infection                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 1            |
| Escherichia urinary tract infection             |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Candida pneumonia                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Arthritis bacterial                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Urinary tract infection bacterial               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Citrobacter sepsis                              |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Clostridium difficile infection                 |                  |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Helicobacter infection                          |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Subdiaphragmatic abscess                        |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Emphysematous cystitis                          |                  |                |                  |



|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                                   | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Staphylococcal sepsis   |                  |                |                  |
| subjects affected / exposed                                   | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Psoas abscess   |                  |                |                  |
| subjects affected / exposed                                   | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 1            |
| Infective exacerbation of chronic obstructive airways disease |                  |                |                  |
| subjects affected / exposed                                   | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 5 / 2993 (0.17%) |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 5            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 1            |
| Infective tenosynovitis                                       |                  |                |                  |
| subjects affected / exposed                                   | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Biliary sepsis  |                  |                |                  |
| subjects affected / exposed                                   | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Abdominal sepsis  |                  |                |                  |
| subjects affected / exposed                                   | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Staphylococcal infection                                      |                  |                |                  |
| subjects affected / exposed                                   | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0          | 0 / 0            |
| Intervertebral discitis                                       |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diabetic foot infection                         |                  |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%) | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Abdominal abscess                               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Bacterial infection                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pneumonia bacterial                             |                  |                |                  |
| subjects affected / exposed                     | 7 / 2993 (0.23%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 0            |
| Clostridial infection                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Escherichia infection                           |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastroenteritis bacterial                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Respiratory syncytial virus infection           |                  |                |                  |

|   |                  |                |                   |
|---|------------------|----------------|-------------------|
| subjects affected / exposed                     | 2 / 2993 (0.07%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Biliary tract infection                         |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Parainfluenzae virus infection                  |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Respiratory tract infection viral               |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Respiratory tract infection                     |                  |                |                   |
| subjects affected / exposed                     | 8 / 2993 (0.27%) | 0 / 15 (0.00%) | 10 / 2993 (0.33%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0          | 0 / 1             |
| Cholecystitis infective                         |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Infective spondylitis                           |                  |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Acarodermatitis                                 |                  |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0             |
| Enterocolitis bacterial                         |                  |                |                   |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Tongue abscess                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Post procedural infection                       |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Rotavirus infection                             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Gastrointestinal viral infection                |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Infectious pleural effusion                     |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Streptococcal endocarditis                      |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Candida infection                               |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Meningoencephalitis viral                       |                  |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Medical device site infection                   |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Medical device site joint infection             |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Systemic infection                              |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Pulmonary paracoccidioidomycosis                |                  |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Vascular device infection                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| H3N2 influenza                                  |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Large intestine infection                       |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Infected gouty tophus                           |                  |                |                  |

|   |                   |                |                   |
|---|-------------------|----------------|-------------------|
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| COVID-19  |                   |                |                   |
| subjects affected / exposed                     | 69 / 2993 (2.31%) | 0 / 15 (0.00%) | 71 / 2993 (2.37%) |
| occurrences causally related to treatment / all | 0 / 69            | 0 / 0          | 0 / 73            |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 0          | 0 / 14            |
| Diverticulitis intestinal perforated            |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| COVID-19 pneumonia                              |                   |                |                   |
| subjects affected / exposed                     | 28 / 2993 (0.94%) | 0 / 15 (0.00%) | 30 / 2993 (1.00%) |
| occurrences causally related to treatment / all | 0 / 28            | 0 / 0          | 0 / 30            |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 0          | 0 / 9             |
| Suspected COVID-19                              |                   |                |                   |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0             |
| SARS-CoV-2 sepsis                               |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Norovirus infection                             |                   |                |                   |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Klebsiella urinary tract infection              |                   |                |                   |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0             |
| Metabolism and nutrition disorders              |                   |                |                   |
| Alkalosis hypochloraemic                        |                   |                |                   |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Cachexia  |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1            |
| Dehydration                                     |                   |                |                  |
| subjects affected / exposed                     | 14 / 2993 (0.47%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 1 / 16            | 0 / 0          | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0          | 0 / 0            |
| Diabetes mellitus                               |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Diabetes mellitus inadequate control            |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Diabetic ketoacidosis                           |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Electrolyte imbalance                           |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Failure to thrive                               |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Gout  |                   |                |                  |

|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 8 / 2993 (0.27%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 2 / 10           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hyperglycaemia                                  |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hyperkalaemia                                   |                   |                |                  |
| subjects affected / exposed                     | 19 / 2993 (0.63%) | 0 / 15 (0.00%) | 6 / 2993 (0.20%) |
| occurrences causally related to treatment / all | 15 / 19           | 0 / 0          | 4 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypernatraemia                                  |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypervolaemia                                   |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypocalcaemia                                   |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypoglycaemia                                   |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypokalaemia                                    |                   |                |                  |
| subjects affected / exposed                     | 3 / 2993 (0.10%)  | 0 / 15 (0.00%) | 9 / 2993 (0.30%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0          | 0 / 11           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hyponatraemia                                   |                   |                |                  |



|   |                   |                |                  |
|---|-------------------|----------------|------------------|
| subjects affected / exposed                     | 10 / 2993 (0.33%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 4 / 11            | 0 / 0          | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Hypovolaemia                                    |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Iron deficiency                                 |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Lactic acidosis                                 |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Marasmus  |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 1 / 2993 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 1            |
| Metabolic acidosis                              |                   |                |                  |
| subjects affected / exposed                     | 2 / 2993 (0.07%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0          | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Mineral metabolism disorder                     |                   |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%)  | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Decreased appetite                              |                   |                |                  |
| subjects affected / exposed                     | 0 / 2993 (0.00%)  | 0 / 15 (0.00%) | 2 / 2993 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          | 0 / 0            |
| Type 2 diabetes mellitus                        |                   |                |                  |

|   |                  |                |                  |
|---|------------------|----------------|------------------|
| subjects affected / exposed                     | 4 / 2993 (0.13%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Diabetic metabolic decompensation               |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 3 / 2993 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |
| Adult failure to thrive                         |                  |                |                  |
| subjects affected / exposed                     | 1 / 2993 (0.03%) | 0 / 15 (0.00%) | 0 / 2993 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0          | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          | 0 / 0            |

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

| <b>Non-serious adverse events</b>                     | Finerenone (BAY94-8862) | Never received treatment | Placebo              |
|---|-------------------------|--------------------------|----------------------|
| Total subjects affected by non-serious adverse events |                         |                          |                      |
| subjects affected / exposed                           | 1317 / 2993 (44.00%)    | 0 / 15 (0.00%)           | 1228 / 2993 (41.03%) |
| Investigations  |                         |                          |                      |
| Glomerular filtration rate decreased                  |                         |                          |                      |
| subjects affected / exposed                           | 156 / 2993 (5.21%)      | 0 / 15 (0.00%)           | 107 / 2993 (3.58%)   |
| occurrences (all)                                     | 219                     | 0                        | 144                  |
| Vascular disorders                                    |                         |                          |                      |
| Hypertension  |                         |                          |                      |
| subjects affected / exposed                           | 103 / 2993 (3.44%)      | 0 / 15 (0.00%)           | 179 / 2993 (5.98%)   |
| occurrences (all)                                     | 121                     | 0                        | 215                  |
| Hypotension   |                         |                          |                      |
| subjects affected / exposed                           | 210 / 2993 (7.02%)      | 0 / 15 (0.00%)           | 128 / 2993 (4.28%)   |
| occurrences (all)                                     | 240                     | 0                        | 143                  |
| Cardiac disorders                                     |                         |                          |                      |
| Cardiac failure                                       |                         |                          |                      |
| subjects affected / exposed                           | 116 / 2993 (3.88%)      | 0 / 15 (0.00%)           | 168 / 2993 (5.61%)   |
| occurrences (all)                                     | 143                     | 0                        | 218                  |
| Nervous system disorders                              |                         |                          |                      |
| Dizziness   |                         |                          |                      |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 170 / 2993 (5.68%)<br>198                                  | 0 / 15 (0.00%)<br>0                            | 137 / 2993 (4.58%)<br>158                                  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 169 / 2993 (5.65%)<br>193                                  | 0 / 15 (0.00%)<br>0                            | 162 / 2993 (5.41%)<br>178                                  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 167 / 2993 (5.58%)<br>208                                  | 0 / 15 (0.00%)<br>0                            | 129 / 2993 (4.31%)<br>157                                  |
| Renal and urinary disorders<br>Renal impairment<br>subjects affected / exposed<br>occurrences (all)   | 193 / 2993 (6.45%)<br>232                                  | 0 / 15 (0.00%)<br>0                            | 110 / 2993 (3.68%)<br>127                                  |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 292 / 2993 (9.76%)<br>301<br><br>150 / 2993 (5.01%)<br>184 | 0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0 | 297 / 2993 (9.92%)<br>318<br><br>149 / 2993 (4.98%)<br>194 |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all) | 252 / 2993 (8.42%)<br>348<br><br>88 / 2993 (2.94%)<br>105  | 0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0 | 107 / 2993 (3.58%)<br>139<br><br>196 / 2993 (6.55%)<br>255 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 21 September 2020 | addressed requests from health authorities   |
| 16 May 2022       | altered certain secondary efficacy endpoints of the study: • The secondary efficacy variable on sustained eGFR decrease was changed from $\geq 40\%$ to $\geq 50\%$ based on data from the FIGARO-DKD and FIDELIO-DKD studies. • Change in NYHA class from baseline was removed from exploratory endpoints. Total HF events and improvement in NYHA class from baseline to Month 12 were added as secondary endpoints due to their clinical significance. • Change in UACR from baseline and time to first occurrence of the following composite endpoint: sustained decrease in eGFR $\geq 57\%$ relative to baseline over at least 4 weeks, or sustained eGFR decline to $<15$ mL/min/1.73 m <sup>2</sup> or initiation of dialysis or renal transplantation, were added as exploratory endpoints to compare the results with existing data from FIGARO-DKD and FIDELIO-DKD. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported