



## Clinical trial results:

**A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus (T2DM) patients with increased cardiovascular risk**

### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2009-016178-33                            |
| Trial protocol           | NL DK ES BE FR IT HU PT GB AT GR PL EE CZ |
| Global end of trial date | 13 April 2015                             |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 29 April 2016 |
| First version publication date | 29 April 2016 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 1245.25 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01131676 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Boehringer Ingelheim   |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216   |
| Public contact               | QRPE Processes and Systems Coordination,<br>Clinical Trial Information Disclosure, Boehringer Ingelheim, +1<br>800 2430127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | QRPE Processes and Systems Coordination,<br>Clinical Trial Information Disclosure, Boehringer Ingelheim, +1<br>800 2430127, clintrriage.rdg@boehringer-ingelheim.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 13 August 2015 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 13 April 2015  |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 April 2015  |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this event driven study is to determine non inferiority (non inferiority margin of 1.3) of the treatment with two pooled doses (10mg q.d and 25 mg q.d.) of BI 10773 versus placebo on the composite of 3 Major Adverse Cardiovascular Events (MACE): cardiovascular death, non fatal stroke and nonfatal myocardial infarction in patients with type 2 diabetes mellitus and increased cardiovascular risk.

Protection of trial subjects:

Monitoring of all patients was performed in accordance with protocol. All subjects were free to withdraw at any time for any reason given.

Background therapy:

Standard care therapy for type 2 diabetes and cardiovascular disease .

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 26 August 2010 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |   |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Australia: 41                               |
| Country: Number of subjects enrolled | Canada: 246                                 |
| Country: Number of subjects enrolled | New Zealand: 25                             |
| Country: Number of subjects enrolled | United States: 2352                         |
| Country: Number of subjects enrolled | Hong Kong: 63                               |
| Country: Number of subjects enrolled | India: 280                                  |
| Country: Number of subjects enrolled | Indonesia: 71                               |
| Country: Number of subjects enrolled | Japan: 103                                  |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 494 |
| Country: Number of subjects enrolled | Malaysia: 322                               |
| Country: Number of subjects enrolled | Philippines: 366                            |
| Country: Number of subjects enrolled | Singapore: 34                               |
| Country: Number of subjects enrolled | Sri Lanka: 113                              |
| Country: Number of subjects enrolled | Taiwan: 223                                 |
| Country: Number of subjects enrolled | Thailand: 124                               |
| Country: Number of subjects enrolled | Argentina: 395                              |
| Country: Number of subjects enrolled | Brazil: 909                                 |
| Country: Number of subjects enrolled | Colombia: 163                               |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Mexico: 140             |
| Country: Number of subjects enrolled | Peru: 244               |
| Country: Number of subjects enrolled | South Africa: 563       |
| Country: Number of subjects enrolled | Austria: 216            |
| Country: Number of subjects enrolled | Belgium: 222            |
| Country: Number of subjects enrolled | Croatia: 220            |
| Country: Number of subjects enrolled | Czech Republic: 26      |
| Country: Number of subjects enrolled | Denmark: 144            |
| Country: Number of subjects enrolled | Estonia: 52             |
| Country: Number of subjects enrolled | France: 144             |
| Country: Number of subjects enrolled | Georgia: 196            |
| Country: Number of subjects enrolled | Greece: 135             |
| Country: Number of subjects enrolled | Hungary: 318            |
| Country: Number of subjects enrolled | Israel: 172             |
| Country: Number of subjects enrolled | Italy: 258              |
| Country: Number of subjects enrolled | Netherlands: 171        |
| Country: Number of subjects enrolled | Norway: 131             |
| Country: Number of subjects enrolled | Poland: 312             |
| Country: Number of subjects enrolled | Portugal: 272           |
| Country: Number of subjects enrolled | Romania: 203            |
| Country: Number of subjects enrolled | Russian Federation: 437 |
| Country: Number of subjects enrolled | Spain: 298              |
| Country: Number of subjects enrolled | Ukraine: 190            |
| Country: Number of subjects enrolled | United Kingdom: 143     |
| Worldwide total number of subjects   | 11531                   |
| EEA total number of subjects         | 3265                    |

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)                      | 6419 |
| From 65 to 84 years                       | 5060 |
| 85 years and over                         | 52   |

## Subject disposition

### Recruitment

Recruitment details:

Patients randomised to treatments Placebo, Empagliflozin 10 mg, Empagliflozin 25 mg in a 1:1:1 ratio. Age for one subject was missing, since EudraCT does not support missing category, the same subject is considered under 18-64 age-group.

### Pre-assignment

Screening details:

All subjects were screened for eligibility considering the protocol defined inclusion/exclusion criteria to participate in the trial.

### Period 1

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

Blinding implementation details:

Randomisation stratified by: BMI at randomisation ( $<30$  or  $\geq 30$  kg/m<sup>2</sup>), HbA1c at screening ( $<8.5\%$  or  $\geq 8.5\%$ ); geographical region (North America including Australia and New Zealand, Latin America, Europe, Africa, Asia); renal function at screening (normal:  $\text{eGFR} \geq 90$  mL/min, mild impairment:  $60 \text{ mL/min} \leq \text{eGFR} \leq 89$  mL/min, moderate impairment:  $30 \text{ mL/min} \leq \text{eGFR} \leq 59$  mL/min).

### Arms

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

Arm description:

Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily). 4 subjects randomised to Placebo were not treated. Although actual number of subjects started is 2337, 2333 were reported to follow the primary analysis set.

|  |                    |
|--|--------------------|
| 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:

Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily).

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Empagliflozin 10 mg |
|------------------|---------------------|

Arm description:

Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily). 2 subjects randomised to Empagliflozin 10 mg were not treated. Although actual number of subjects started is 2347, 2345 were reported to follow the primary analysis set.

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

Dosage and administration details:

Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily)

|   |                     |
|---|---------------------|
| <b>Arm title</b>  | Empagliflozin 25 mg |
| Arm description:  |                     |
| Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily).<br>2 subjects randomised to Empagliflozin 25 mg were not treated. Although actual number of subjects started is 2344, 2342 were reported to follow the primary analysis set. |                     |
| Arm type  | Experimental        |
| Investigational medicinal product name  | Empagliflozin       |
| Investigational medicinal product code  |                     |
| Other name  |                     |
| Pharmaceutical forms  | Film-coated tablet  |
| Routes of administration  | Oral use            |

**Dosage and administration details:**

Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily)

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
|---|---------|---------------------|---------------------|
| Started   | 2333    | 2345                | 2342                |
| Completed   | 1650    | 1790                | 1800                |
| Not completed                                       | 683     | 555                 | 542                 |
| Adverse event, serious fatal                        | 102     | 89                  | 71                  |
| Other than those specified                          | 162     | 142                 | 125                 |
| Non compliant with protocol                         | 15      | 15                  | 12                  |
| Adverse event, non-fatal                            | 201     | 178                 | 202                 |
| Study drug stopped, reason missing                  | 5       | 3                   | 4                   |
| Refusal to continue, not due to AE                  | 172     | 118                 | 122                 |
| Lost to follow-up                                   | 15      | 9                   | 6                   |
| Lack of efficacy                                    | 11      | 1                   | -                   |

**Notes:**

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

**Period 2**

|                              |  |
|------------------------------|--|
| Period 2 title               | Discontinuation from study (Treated set)     |
| Is this the baseline period? | No   |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

**Arms**

|                              |    |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

|   |                     |
|---|---------------------|
| <b>Arm title</b>  | Placebo             |
| Arm description:  |                     |
| Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet 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:  |                     |
| Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily)      |                     |
| <b>Arm title</b>  | Empagliflozin 10 mg |
| Arm description:  |                     |
| Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily) |                     |
| Arm type  | Experimental        |
| Investigational medicinal product name  | Empagliflozin       |
| Investigational medicinal product code  |                     |
| Other name  |                     |
| Pharmaceutical forms  | Film-coated tablet  |
| Routes of administration  | Oral use            |
| Dosage and administration details:  |                     |
| Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily) |                     |
| <b>Arm title</b>  | Empagliflozin 25 mg |
| Arm description:  |                     |
| Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily) |                     |
| Arm type  | Experimental        |
| Investigational medicinal product name  | Empagliflozin       |
| Investigational medicinal product code  |                     |
| Other name  |                     |
| Pharmaceutical forms  | Film-coated tablet  |
| Routes of administration  | Oral use            |
| Dosage and administration details:  |                     |
| Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily) |                     |

| <b>Number of subjects in period 2</b>    | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
|--|---------|---------------------|---------------------|
| Started                                  | 2333    | 2345                | 2342                |
| Final vital status (VS) available        | 2316    | 2324                | 2327                |
| Completed                                | 2266    | 2264                | 2279                |
| Not completed                            | 67      | 81                  | 63                  |
| Site closure:Final VS not available (NA) | 5       | 9                   | 7                   |
| Consent withdrawn:Final VS not available | 8       | 6                   | 5                   |
| Site closure: Final VS available         | 20      | 21                  | 19                  |
| Lost to FU for 3P-MACE:Final VS NA       | 4       | 4                   | 2                   |
| Lost to FU for 3PMACE:Final VS available | 7       | 6                   | 5                   |

|                                       |    |    |    |
|---------------------------------------|----|----|----|
| Consent withdrawn: Final VS available | 23 | 35 | 25 |
|---------------------------------------|----|----|----|

## Baseline characteristics

### Reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Placebo             |
| Reporting group description:  |                     |
| Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily).<br>4 subjects randomised to Placebo were not treated. Although actual number of subjects started is 2337, 2333 were reported to follow the primary analysis set.                  |                     |
| Reporting group title   | Empagliflozin 10 mg |
| Reporting group description:  |                     |
| Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily).<br>2 subjects randomised to Empagliflozin 10 mg were not treated. Although actual number of subjects started is 2347, 2345 were reported to follow the primary analysis set. |                     |
| Reporting group title   | Empagliflozin 25 mg |
| Reporting group description:  |                     |
| Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily).<br>2 subjects randomised to Empagliflozin 25 mg were not treated. Although actual number of subjects started is 2344, 2342 were reported to follow the primary analysis set. |                     |

| Reporting group values             | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
|------------------------------------|---------|---------------------|---------------------|
| Number of subjects                 | 2333    | 2345                | 2342                |
| Age categorical<br>Units: Subjects |         |                     |                     |

|   |       |       |       |
|---|-------|-------|-------|
| Age Continuous  |       |       |       |
| Treated set (TS): Consists of all randomised patients who received at least 1 dose of study medication. Patients were assigned to treatment groups according to the randomisation scheme. |       |       |       |
| Units: years  |       |       |       |
| arithmetic mean   | 63.2  | 63    | 63.2  |
| standard deviation  | ± 8.8 | ± 8.6 | ± 8.6 |
| Gender, Male/Female<br>Units: participants  |       |       |       |
| Female  | 653   | 692   | 659   |
| Male  | 1680  | 1653  | 1683  |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 7020  |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |      |  |  |
|---|------|--|--|
| Age Continuous  |      |  |  |
| Treated set (TS): Consists of all randomised patients who received at least 1 dose of study medication. Patients were assigned to treatment groups according to the randomisation scheme. |      |  |  |
| Units: years  |      |  |  |
| arithmetic mean   | -    |  |  |
| standard deviation  |      |  |  |
| Gender, Male/Female<br>Units: participants  |      |  |  |
| Female  | 2004 |  |  |
| Male  | 5016 |  |  |



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**Subject analysis sets**

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|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | All Empagliflozin |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

Patients who received either 10 mg or 25 mg of empagliflozin were pooled into a common empagliflozin treatment group.

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|                               |                   |  |  |
|-------------------------------|-------------------|--|--|
| <b>Reporting group values</b> | All Empagliflozin |  |  |
| Number of subjects            | 4687              |  |  |
| Age categorical               |                   |  |  |
| Units: Subjects               |                   |  |  |

|   |       |  |  |
|---|-------|--|--|
| Age Continuous  |       |  |  |
| Treated set (TS): Consists of all randomised patients who received at least 1 dose of study medication. Patients were assigned to treatment groups according to the randomisation scheme. |       |  |  |
| Units: years  |       |  |  |
| arithmetic mean   | 63.1  |  |  |
| standard deviation  | ± 8.6 |  |  |
| Gender, Male/Female   |       |  |  |
| Units: participants   |       |  |  |
| Female  | 1351  |  |  |
| Male  | 3336  |  |  |

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## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Placebo             |
| Reporting group description:<br>Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily).<br>4 subjects randomised to Placebo were not treated. Although actual number of subjects started is 2337, 2333 were reported to follow the primary analysis set.                  |                     |
| Reporting group title   | Empagliflozin 10 mg |
| Reporting group description:<br>Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily).<br>2 subjects randomised to Empagliflozin 10 mg were not treated. Although actual number of subjects started is 2347, 2345 were reported to follow the primary analysis set. |                     |
| Reporting group title   | Empagliflozin 25 mg |
| Reporting group description:<br>Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily).<br>2 subjects randomised to Empagliflozin 25 mg were not treated. Although actual number of subjects started is 2344, 2342 were reported to follow the primary analysis set. |                     |
| Reporting group title   | Placebo             |
| Reporting group description:<br>Oral administration of Placebo matching empagliflozin 10 mg or 25 mg (1 tablet once daily)  |                     |
| Reporting group title   | Empagliflozin 10 mg |
| Reporting group description:<br>Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily)   |                     |
| Reporting group title   | Empagliflozin 25 mg |
| Reporting group description:<br>Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily)   |                     |
| Subject analysis set title  | All Empagliflozin   |
| Subject analysis set type   | Full analysis       |
| Subject analysis set description:<br>Patients who received either 10 mg or 25 mg of empagliflozin were pooled into a common empagliflozin treatment group.  |                     |

### **Primary: Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (3-point MACE): CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), and non-fatal stroke.**

|  |   |
|--|---|
| End point title  | Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (3-point MACE): CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), and non-fatal stroke. |
| End point description:<br>Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (3-point major adverse cardiovascular events (MACE)): cardiovascular (CV) death (including fatal stroke and fatal myocardial infarction (MI)), non-fatal MI (excluding silent MI), and non-fatal stroke.<br><br>Percentage of patients with the event are presented. |   |
| End point type   | Primary   |
| End point timeframe:<br>From randomisation to individual end of observation, up to 4.6 years   |   |

| End point values                  | Placebo             | Empagliflozin 10 mg | Empagliflozin 25 mg | All Empagliflozin    |
|-----------------------------------|---------------------|---------------------|---------------------|----------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     | Subject analysis set |
| Number of subjects analysed       | 2333 <sup>[1]</sup> | 2345 <sup>[2]</sup> | 2342 <sup>[3]</sup> | 4687 <sup>[4]</sup>  |
| Units: percentage of participants |                     |                     |                     |                      |
| number (not applicable)           | 12.1                | 10.4                | 10.5                | 10.5                 |

Notes:

[1] - TS (evaluable cases)

[2] - TS (evaluable cases)

[3] - TS (evaluable cases)

[4] - TS (evaluable cases)

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Primary objective was to establish the non-inferiority of All empagliflozin relative to placebo for time to first 3-point MACE. A 4-step hierarchical testing strategy was followed for the non-inferiority test of the primary endpoint and then the key secondary endpoint, each at a margin of 1.3, followed by test of superiority of primary and key secondary endpoints.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 7020                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[5]</sup> |
| P-value                                 | < 0.0001 <sup>[6]</sup>        |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.86                           |
| Confidence interval                     |                                |
| level                                   | 95.02 %                        |
| sides                                   | 2-sided                        |
| lower limit                             | 0.74                           |
| upper limit                             | 0.99                           |

Notes:

[5] - The non-inferiority margin was chosen as 1.3 based on Food and Drug Administration (FDA) Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes .

[6] - One-sided test with alpha = 0.0249.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

| Statistical analysis title              | Statistical Analysis 2         |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 7020                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0382 <sup>[7]</sup>        |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.86                           |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95.02 % |
| sides               | 2-sided |
| lower limit         | 0.74    |
| upper limit         | 0.99    |

Notes:

[7] - Two-sided test with  $\alpha=0.0498$ .

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

**Secondary: Percentage of participants with composite of all events adjudicated (4-point MACE):CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke and hospitalization for unstable angina pectoris**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with composite of all events adjudicated (4-point MACE):CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke and hospitalization for unstable angina pectoris |
|-----------------|--|

End point description:

The composite of all events adjudicated (4-point MACE): cardiovascular death (including fatal stroke and fatal myocardial infarction), non-fatal myocardial infarction (excluding silent MI), non-fatal stroke and hospitalization for unstable angina pectoris. This is a key secondary endpoint of the trial.

Percentage of patients with the event are presented.

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

End point timeframe:

From randomisation to individual end of observation, up to 4.6 years

| End point values                  | Placebo             | Empagliflozin 10 mg | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|---------------------|---------------------|----------------------|----------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 2333 <sup>[8]</sup> | 2345 <sup>[9]</sup> | 2342 <sup>[10]</sup> | 4687 <sup>[11]</sup> |
| Units: percentage of participants |                     |                     |                      |                      |
| number (not applicable)           | 14.3                | 12.8                | 12.8                 | 12.8                 |

Notes:

[8] - TS (evaluable cases)

[9] - TS (evaluable cases)

[10] - TS (evaluable cases)

[11] - TS (evaluable cases)

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

A 4-step hierarchical testing strategy was followed for the non-inferiority test of the primary endpoint and then the key secondary endpoint, each at a margin of 1.3, followed by test of superiority of primary and key secondary endpoints.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Placebo v All Empagliflozin |
|-------------------|-----------------------------|

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 7020                            |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[12]</sup> |
| P-value                                 | < 0.0001 <sup>[13]</sup>        |
| Method                                  | Cox proportional hazards model  |
| Parameter estimate                      | Hazard ratio (HR)               |
| Point estimate                          | 0.89                            |
| Confidence interval                     |                                 |
| level                                   | 95.02 %                         |
| sides                                   | 2-sided                         |
| lower limit                             | 0.78                            |
| upper limit                             | 1.01                            |

Notes:

[12] - The non-inferiority margin was chosen as 1.3 based on Food and Drug Administration (FDA) Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

[13] - One-sided test with alpha = 0.0249.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

A 4-step hierarchical testing strategy was followed for the non-inferiority test of the primary endpoint and then the key secondary endpoint, each at a margin of 1.3, followed by test of superiority of primary and key secondary endpoints.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 7020                           |
| Analysis specification                  | Post-hoc                       |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0795 <sup>[14]</sup>       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.89                           |
| Confidence interval                     |                                |
| level                                   | 95.02 %                        |
| sides                                   | 2-sided                        |
| lower limit                             | 0.78                           |
| upper limit                             | 1.01                           |

Notes:

[14] - Two-sided test with alpha=0.0498.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

## Secondary: Percentage of participants with silent MI

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with silent MI |
|-----------------|---|

End point description:

Silent MI; defined as presence in the ECG of:

- Any Q-wave in leads V2-V3  $\geq 0.02$  seconds or QS complex in leads V2 and V3
- Q-wave  $\geq 0.03$  seconds and  $\geq 0.1$  mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
- R-wave  $\geq 0.04$  seconds in V1-V2 and R/S  $\geq 1$  with a concordant positive T-wave in the absence of a conduction defect.

It was also required that there had been no adjudicated and confirmed event of either acute MI, hospitalisation for unstable angina, coronary revascularisation procedures or stent thrombosis following randomisation up to and including the date of the specified ECG measurement.

Percentage of patients with the event are presented.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From randomisation to individual end of observation, up to 4.6 years |           |

| End point values                  | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 1211 <sup>[15]</sup> | 1174 <sup>[16]</sup> | 1204 <sup>[17]</sup> | 2378 <sup>[18]</sup> |
| Units: percentage of participants |                      |                      |                      |                      |
| number (not applicable)           | 1.2                  | 1.6                  | 1.6                  | 1.6                  |

Notes:

[15] - TS (evaluable cases)

[16] - TS (evaluable cases)

[17] - TS (evaluable cases)

[18] - TS (evaluable cases)

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title              | Statistical analysis 1         |
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 3589                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.4172 <sup>[19]</sup>       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 1.28                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.7                            |
| upper limit                             | 2.33                           |

Notes:

[19] - Two-sided test with alpha = 0.05.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo

### Secondary: Percentage of participants with heart failure requiring hospitalisation (adjudicated)

|  |   |
|--|---|
| End point title  | Percentage of participants with heart failure requiring hospitalisation (adjudicated) |
| End point description:   |   |
| Heart failure requiring hospitalisation (adjudicated).<br>Percentage of patients with the event are presented. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From randomisation to individual end of observation, up to 4.6 years   |   |

| End point values                  | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 2333 <sup>[20]</sup> | 2345 <sup>[21]</sup> | 2342 <sup>[22]</sup> | 4687 <sup>[23]</sup> |
| Units: percentage of participants |                      |                      |                      |                      |
| number (not applicable)           | 4.1                  | 2.6                  | 2.8                  | 2.7                  |

Notes:

[20] - TS (evaluable cases)

[21] - TS (evaluable cases)

[22] - TS (evaluable cases)

[23] - TS (evaluable cases)

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1         |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 7020                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.0017 <sup>[24]</sup>       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.65                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.5                            |
| upper limit                             | 0.85                           |

Notes:

[24] - Two-sided test with alpha = 0.05.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

## Secondary: Percentage of participants with new onset albuminuria

|  |   |
|--|---|
| End point title  | Percentage of participants with new onset albuminuria |
| End point description:   |   |
| New onset albuminuria defined as urine albumin / creatinine ratio (UACR) $\geq 30$ mg/g.<br>Percentage of patients with the event are presented. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From randomisation to individual end of observation, up to 4.6 years   |   |

| End point values                  | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 1374 <sup>[25]</sup> | 1403 <sup>[26]</sup> | 1376 <sup>[27]</sup> | 2779 <sup>[28]</sup> |
| Units: percentage of participants |                      |                      |                      |                      |
| number (not applicable)           | 51.2                 | 51.5                 | 51.5                 | 51.5                 |

Notes:

[25] - TS (evaluable cases)

[26] - TS (evaluable cases)

[27] - TS (evaluable cases)

[28] - TS (evaluable cases)

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1         |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 4153                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.2547 <sup>[29]</sup>       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.95                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.87                           |
| upper limit                             | 1.04                           |

Notes:

[29] - Two-sided test with alpha = 0.05.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo

## Secondary: Percentage of participants with new onset macroalbuminuria

|                        |  |
|------------------------|--|
| End point title        | Percentage of participants with new onset macroalbuminuria           |
| End point description: |  |
|                        | New onset macroalbuminuria defined as UACR >300 mg/g.                |
|                        | Percentage of patients with the event are presented.                 |
| End point type         | Secondary  |
| End point timeframe:   |  |
|                        | From randomisation to individual end of observation, up to 4.6 years |

| End point values                  | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 2033 <sup>[30]</sup> | 2037 <sup>[31]</sup> | 2054 <sup>[32]</sup> | 4091 <sup>[33]</sup> |
| Units: percentage of participants |                      |                      |                      |                      |
| number (not applicable)           | 16.2                 | 10.9                 | 11.5                 | 11.2                 |



Notes:

[30] - TS (evaluable cases)

[31] - TS (evaluable cases)

[32] - TS (evaluable cases)

[33] - TS (evaluable cases)

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1         |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 6124                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | < 0.0001 [34]                  |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.62                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.54                           |
| upper limit                             | 0.72                           |

Notes:

[34] - Two-sided test with alpha = 0.05.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

## Secondary: Percentage of participants with composite microvascular outcome

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with composite microvascular outcome |
|-----------------|---|

End point description:

Composite microvascular outcome defined as:

- Initiation of retinal photocoagulation
- Vitreous haemorrhage
- Diabetes-related blindness, or
- New or worsening nephropathy defined as:
  - New onset of macroalbuminuria; or
  - Doubling of serum creatinine level accompanied by an eGFR (based on modification of diet in renal disease (MDRD) formula)  $\leq 45$  mL/min/1.73m<sup>2</sup>; or
  - Initiation of continuous renal replacement therapy, or
  - Death due to renal disease.

Percentage of patients with the event are presented.

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

End point timeframe:

From randomisation to individual end of observation, up to 4.6 years

| End point values                  | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  | All Empagliflozin    |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed       | 2068 <sup>[35]</sup> | 2057 <sup>[36]</sup> | 2075 <sup>[37]</sup> | 4132 <sup>[38]</sup> |
| Units: percentage of participants |                      |                      |                      |                      |
| number (not applicable)           | 20.5                 | 13.9                 | 14.1                 | 14                   |

Notes:

[35] - TS (evaluable cases)

[36] - TS (evaluable cases)

[37] - TS (evaluable cases)

[38] - TS (evaluable cases)

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1         |
|---|--------------------------------|
| Comparison groups                       | Placebo v All Empagliflozin    |
| Number of subjects included in analysis | 6200                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | < 0.0001 <sup>[39]</sup>       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.62                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.54                           |
| upper limit                             | 0.7                            |

Notes:

[39] - Two-sided test with alpha = 0.05.

Cox proportional hazards model with factors for treatment, age, gender, categorised BMI, HbA1c, eGFR and geographical region.

All Empagliflozin divided by Placebo.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs, serious and non-serious, occurring during the course of the clinical trial (adverse events up until treatment stop + 7 days); Up to 4.6 years

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Oral administration of Placebo matching empagliflozin 10 mg and 25 mg (1 tablet once daily)

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

Reporting group description:

Oral administration of Empagliflozin 10 mg (BI 10773) film coated tablets (1 tablet once daily)

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Empagliflozin 25 mg |
|-----------------------|---------------------|

Reporting group description:

Oral administration of Empagliflozin 25 mg (BI 10773) film coated tablets (1 tablet once daily)

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | All Empagliflozin |
|-----------------------|-------------------|

Reporting group description:

Patients who received either 10 mg or 25 mg of empagliflozin were pooled into a common empagliflozin treatment group for the purposes of the primary analysis.

| Serious adverse events  | Placebo             | Empagliflozin 10 mg | Empagliflozin 25 mg |
|---|---------------------|---------------------|---------------------|
| Total subjects affected by serious adverse events                   |                     |                     |                     |
| subjects affected / exposed   | 988 / 2333 (42.35%) | 876 / 2345 (37.36%) | 913 / 2342 (38.98%) |
| number of deaths (all causes)                                       | 119                 | 97                  | 79                  |
| number of deaths resulting from adverse events                      | 2                   | 3                   | 1                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                     |                     |
| Acoustic neuroma  |                     |                     |                     |
| subjects affected / exposed   | 0 / 2333 (0.00%)    | 3 / 2345 (0.13%)    | 0 / 2342 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 3               | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               | 0 / 0               |
| Acute lymphocytic leukaemia   |                     |                     |                     |
| subjects affected / exposed   | 0 / 2333 (0.00%)    | 1 / 2345 (0.04%)    | 0 / 2342 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1               | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 1               | 0 / 0               |
| Acute myeloid leukaemia   |                     |                     |                     |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Adenocarcinoma                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Adenocarcinoma gastric                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Adenocarcinoma of colon                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Adenocarcinoma pancreas                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 3 / 2345 (0.13%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 2            |
| Adenoma benign                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anogenital warts                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| B-cell lymphoma                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Basal cell carcinoma                            |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 16 / 2333 (0.69%) | 15 / 2345 (0.64%) | 12 / 2342 (0.51%) |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 17            | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Basosquamous carcinoma                          |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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 hepatic neoplasm                         |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Benign laryngeal neoplasm                       |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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 lung neoplasm                            |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Benign neoplasm of adrenal gland                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Benign neoplasm of bladder                      |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Benign neoplasm of prostate                     |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Benign neoplasm of thyroid gland                |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Benign pancreatic neoplasm                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Benign respiratory tract neoplasm               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 uterine neoplasm                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bile duct cancer                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder cancer                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 2            |
| Bladder cancer recurrent                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder transitional cell carcinoma             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bone cancer                                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bone giant cell tumour benign                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bowen's disease                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Brain neoplasm                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Breast cancer                                   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchial carcinoma                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac myxoma                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Cervix carcinoma                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholesteatoma                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Chronic lymphocytic leukaemia                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Clear cell renal cell carcinoma                 |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colon adenoma                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 cancer                                    |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 5 / 2345 (0.21%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 1            |
| Colon cancer metastatic                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 3            |
| Colon neoplasm                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 adenocarcinoma                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colorectal cancer                               |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endometrial cancer                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Fibroadenoma of breast                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Fibrosarcoma                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Follicular thyroid cancer                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric cancer                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal stromal tumour                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Genital neoplasm malignant female               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemangioma of bone                             |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemangioma of liver                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hepatic neoplasm                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatocellular carcinoma                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 1            |
| Hodgkin's disease stage I                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Intraductal proliferative breast lesion         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Invasive ductal breast carcinoma                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Keratoacanthoma                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large cell lung cancer                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Laryngeal squamous cell carcinoma               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Lipoma  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung adenocarcinoma                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 5 / 2345 (0.21%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 2            |
| Lung cancer metastatic                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Lung carcinoma cell type unspecified stage III  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 malignant                         |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 4            |
| Lung squamous cell carcinoma stage III          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Lymphocytic lymphoma                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Lymphoma  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lymphoproliferative disorder                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 melanoma                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Malignant melanoma in situ                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Malignant neoplasm of unknown primary site      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Meningioma                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Malignant neoplasm progression                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 bone                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Metastases to liver                             |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 5 / 2345 (0.21%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 5            | 0 / 5            |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 1            | 0 / 3            |
| Metastases to lung                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Metastases to lymph nodes                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 peritoneum                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Metastases to neck                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 pleura                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Metastasis                                      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Metastatic malignant melanoma                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Myelodysplastic syndrome                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Metastatic renal cell carcinoma                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neuroendocrine carcinoma                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nasopharyngeal cancer                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1            |
| Non-Hodgkin's lymphoma stage IV                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neuroendocrine carcinoma of the skin            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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-Hodgkin's lymphoma                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            | 0 / 0            |
| Oesophageal carcinoma                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| POEMS syndrome                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatic carcinoma                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 2            | 0 / 1            |
| Papillary serous endometrial carcinoma          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Papillary thyroid cancer                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Parathyroid tumour benign                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pituitary tumour benign                         |                  |                  |                  |

|   |                  |                   |                  |
|---|------------------|-------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Penile squamous cell carcinoma                  |                  |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Plasma cell myeloma                             |                  |                   |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%)  | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Prostate cancer                                 |                  |                   |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 11 / 2345 (0.47%) | 9 / 2342 (0.38%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 11            | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             | 0 / 0            |
| Rectal adenocarcinoma                           |                  |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 4 / 2345 (0.17%)  | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 2            |
| Prostate cancer recurrent                       |                  |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Prostatic adenoma                               |                  |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Rectal cancer                                   |                  |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| Renal cancer                                    |                  |                   |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 cell carcinoma                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal cancer metastatic                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal cell carcinoma stage I                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 cell carcinoma stage II                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Salivary gland neoplasm                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Salivary gland adenoma                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Skin cancer                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small cell carcinoma                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Sarcoma   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Splenic marginal zone lymphoma                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small cell lung cancer                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Squamous cell carcinoma                         |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 6 / 2345 (0.26%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Squamous cell carcinoma of lung                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            | 0 / 0            |
| Squamous cell carcinoma of skin                 |                  |                  |                  |
| subjects affected / exposed                     | 7 / 2333 (0.30%) | 4 / 2345 (0.17%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 5            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Squamous cell carcinoma of the oral cavity      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Thyroid neoplasm                                |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 neoplasm malignant stage unspecified     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tumour haemorrhage                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 cancer                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 leiomyoma                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 disorders                              |                  |                  |                  |
| Accelerated hypertension                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aneurysm  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Angiopathy                                      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aortic arteriosclerosis                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aortic dissection                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 stenosis                                 |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Arterial disorder                               |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial haemorrhage                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial occlusive disease                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial stenosis                               |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Arteriosclerosis                                |                  |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Arteriovenous fistula                           |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Arteritis                                       |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Deep vein thrombosis                            |                  |                  |                   |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 3 / 2345 (0.13%) | 10 / 2342 (0.43%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Diabetic microangiopathy                        |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0             |
| Embolism arterial                               |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Extremity necrosis                              |                  |                  |                   |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 2333 (0.21%)  | 4 / 2345 (0.17%) | 8 / 2342 (0.34%) |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 5            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Femoral artery embolism                         |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Femoral artery occlusion                        |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 3 / 2345 (0.13%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 5            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Haematoma                                       |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Haemorrhage                                     |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hypertension                                    |                   |                  |                  |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 4 / 2345 (0.17%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 4            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Hypertensive crisis                             |                   |                  |                  |
| subjects affected / exposed                     | 8 / 2333 (0.34%)  | 3 / 2345 (0.13%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Hypotension                                     |                   |                  |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%)  | 5 / 2345 (0.21%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 5            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Hypertensive emergency                          |                   |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hypovolaemic shock                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Iliac artery occlusion                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infarction                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intermittent claudication                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 4 / 2345 (0.17%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ischaemia                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Leriche syndrome                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Malignant hypertension                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Orthostatic hypotension                         |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 3 / 2345 (0.13%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 3             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Peripheral arterial occlusive disease           |                   |                   |                   |
| subjects affected / exposed                     | 23 / 2333 (0.99%) | 28 / 2345 (1.19%) | 30 / 2342 (1.28%) |
| occurrences causally related to treatment / all | 1 / 30            | 1 / 37            | 0 / 38            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Peripheral artery aneurysm                      |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 artery stenosis                      |                   |                   |                   |
| subjects affected / exposed                     | 6 / 2333 (0.26%)  | 3 / 2345 (0.13%)  | 9 / 2342 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 3             | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Peripheral artery thrombosis                    |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Peripheral coldness                             |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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 embolism                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 ischaemia                            |                   |                   |                   |
| subjects affected / exposed                     | 9 / 2333 (0.39%)  | 4 / 2345 (0.17%)  | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 5             | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Peripheral vascular disorder                    |                   |                   |                   |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 8 / 2333 (0.34%) | 3 / 2345 (0.13%) | 6 / 2342 (0.26%) |
| occurrences causally related to treatment / all | 1 / 8            | 0 / 3            | 1 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral venous disease                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Subclavian artery stenosis                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombophlebitis                                |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombophlebitis superficial                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Varicose ulceration                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Varicose vein                                   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 calcification                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular insufficiency                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Venous occlusion                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Venous thrombosis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Venous thrombosis limb                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Coronary angioplasty                            |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Coronary arterial stent insertion               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Coronary artery bypass                          |                  |                  |                  |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| subjects affected / exposed                          | 4 / 2333 (0.17%) | 3 / 2345 (0.13%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Coronary revascularisation                           |                  |                  |                  |
| subjects affected / exposed                          | 5 / 2333 (0.21%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 5            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Fracture treatment                                   |                  |                  |                  |
| subjects affected / exposed                          | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Percutaneous coronary intervention                   |                  |                  |                  |
| subjects affected / exposed                          | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Prophylaxis  |                  |                  |                  |
| subjects affected / exposed                          | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Stent placement                                      |                  |                  |                  |
| subjects affected / exposed                          | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| General disorders and administration site conditions |                  |                  |                  |
| Adverse drug reaction                                |                  |                  |                  |
| subjects affected / exposed                          | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac death  |                  |                  |                  |
| subjects affected / exposed                          | 3 / 2333 (0.13%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all      | 0 / 3            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all           | 0 / 3            | 0 / 4            | 0 / 2            |
| Asthenia   |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 2 / 2345 (0.09%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Chills  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Chest pain                                      |                   |                   |                   |
| subjects affected / exposed                     | 28 / 2333 (1.20%) | 32 / 2345 (1.36%) | 33 / 2342 (1.41%) |
| occurrences causally related to treatment / all | 0 / 31            | 1 / 32            | 0 / 36            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Chest discomfort                                |                   |                   |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%)  | 2 / 2345 (0.09%)  | 3 / 2342 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Death   |                   |                   |                   |
| subjects affected / exposed                     | 12 / 2333 (0.51%) | 10 / 2345 (0.43%) | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 10            | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 12            | 0 / 10            | 0 / 5             |
| Device defective                                |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Device difficult to use                         |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Device deposit issue                            |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Device occlusion                                |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device malfunction                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Dysplasia                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Drug ineffective                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Drowning  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Extravasation                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Fatigue   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gait disturbance                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Feeling abnormal                                |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Generalised oedema                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 physical health deterioration           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Granuloma                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hernia  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Impaired healing                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Implant site necrosis                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Multi-organ failure                             |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1            | 0 / 0            |
| Malaise   |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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                     | 5 / 2333 (0.21%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Non-cardiac chest pain                          |                  |                  |                   |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 5 / 2345 (0.21%) | 15 / 2342 (0.64%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5            | 1 / 15            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Necrobiosis                                     |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Oversensing                                     |                  |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Pacemaker generated arrhythmia                  |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Perforated ulcer                                |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Pain  |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 swelling                             |                  |                  |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Polyp   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyrexia   |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 7 / 2345 (0.30%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stent malfunction                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Strangulated hernia                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sudden death                                    |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 8 / 2345 (0.34%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 1 / 6            | 1 / 8            | 0 / 5            |
| deaths causally related to treatment / all      | 1 / 6            | 1 / 8            | 0 / 5            |
| Sudden cardiac death                            |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            | 0 / 2            |
| Systemic inflammatory response syndrome         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ulcer   |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Immune system disorders                         |                  |                  |                  |
| Anaphylactic reaction                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anaphylactic shock                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Food allergy                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Contrast media allergy                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hypersensitivity                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Iodine allergy                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Social circumstances                            |                  |                  |                  |
| Physical assault                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Reproductive system and breast                  |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| disorders                                       |                  |                  |                   |
| Benign prostatic hyperplasia                    |                  |                  |                   |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 8 / 2345 (0.34%) | 10 / 2342 (0.43%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 8            | 1 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1             |
| Cystocele                                       |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Endometrial hyperplasia                         |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Fibrocystic breast disease                      |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Genital prolapse                                |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Gynaecomastia                                   |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Menorrhagia                                     |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Ovarian cyst                                    |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Prostatism                                      |                  |                  |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostatic obstruction                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Prostatitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Uterine polyp                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 prolapse                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Uterovaginal prolapse                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vaginal prolapse                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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, thoracic and mediastinal disorders |                  |                  |                  |
| Acute pulmonary oedema                          |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 7 / 2345 (0.30%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 1            |
| Acute respiratory distress syndrome             |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Acute respiratory failure                       |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 5 / 2345 (0.21%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 0            |
| Allergic sinusitis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Asthma  |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 5            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Atelectasis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchial disorder                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Bronchial secretion retention                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchiectasis                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchitis chronic                              |                  |                  |                  |

|   |                   |                  |                   |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 2 / 2345 (0.09%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Bronchospasm                                    |                   |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Chronic obstructive pulmonary disease           |                   |                  |                   |
| subjects affected / exposed                     | 11 / 2333 (0.47%) | 6 / 2345 (0.26%) | 10 / 2342 (0.43%) |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 7            | 0 / 14            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Dyspnoea  |                   |                  |                   |
| subjects affected / exposed                     | 14 / 2333 (0.60%) | 6 / 2345 (0.26%) | 9 / 2342 (0.38%)  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 7            | 0 / 9             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Dyspnoea exertional                             |                   |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Emphysema                                       |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Epistaxis                                       |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 3 / 2345 (0.13%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Haemoptysis                                     |                   |                  |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%)  | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Haemothorax                                     |                   |                  |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hydrothorax                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hypoxia   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Idiopathic pulmonary fibrosis                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Interstitial lung disease                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Laryngeal oedema                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung disorder                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung infiltration                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Mediastinal haematoma                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nasal polyps                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Obstructive airways disorder                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Paranasal cyst                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleural effusion                                |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 1 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleural fibrosis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Pleurisy  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleuritic pain                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 aspiration                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Pneumothorax                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Pulmonary arterial hypertension                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 congestion                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| 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 embolism                              |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 0 / 2345 (0.00%) | 6 / 2342 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Pulmonary fibrosis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1            |
| Pulmonary hypertension                          |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary mass                                  |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 oedema                                |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Pulmonary thrombosis                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 toxicity                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 distress                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 arrest                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 failure                             |                  |                  |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0            | 0 / 0            |
| Sinus disorder                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sleep apnoea syndrome                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Status asthmaticus                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 airway obstruction                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vocal cord polyp                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vocal cord thickening                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Psychiatric disorders                           |                  |                  |                  |
| Anxiety   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Completed suicide                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 2 / 2333 (0.09%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Delirium  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Depression                                      |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hallucination                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Insomnia  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Major depression                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mental status changes                           |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rapid eye movements sleep abnormal              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Substance abuse                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Suicidal ideation                               |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Suicide attempt                                 |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0             |
| Hepatobiliary disorders                         |                  |                  |                   |
| Bile duct obstruction                           |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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                     | 0 / 2333 (0.00%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 1 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cholecystitis                                   |                  |                  |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 4 / 2345 (0.17%) | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cholecystitis acute                             |                  |                  |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 7 / 2345 (0.30%) | 6 / 2342 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7            | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cholangitis                                     |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cholelithiasis                                  |                  |                  |                   |
| subjects affected / exposed                     | 7 / 2333 (0.30%) | 9 / 2345 (0.38%) | 12 / 2342 (0.51%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 9            | 1 / 12            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cholecystitis chronic                           |                  |                  |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Gallbladder disorder                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholestasis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic failure                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hepatic steatosis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ischaemic hepatitis                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hepatic function abnormal                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Jaundice cholestatic                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Portal hypertension                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Post cholecystectomy syndrome                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Sphincter of Oddi dysfunction                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Investigations                                  |                  |                  |                  |
| Alanine aminotransferase increased              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Angiogram normal                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Angiogram                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arteriogram coronary                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anticoagulation drug level above therapeutic    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood calcium decreased                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Aspartate aminotransferase increased            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Biopsy lung                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 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 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 creatine phosphokinase increased          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood glucose fluctuation                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 creatinine increased                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood lactate dehydrogenase increased           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood magnesium decreased                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood pressure increased                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Blood urea increased                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood pressure orthostatic decreased            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 murmur                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| C-reactive protein increased                    |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac stress test abnormal                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Catheterisation cardiac                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ejection fraction decreased                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Electrocardiogram T wave inversion              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemoglobin decreased                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic enzyme increased                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Heart rate irregular                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Lipase increased                                |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Liver function test abnormal                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oxygen consumption increased                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Physical examination                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 specific antigen increased            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Scan myocardial perfusion abnormal              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Smear cervix abnormal                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Transaminases increased                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Troponin I increased                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Troponin increased                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Weight decreased                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| White blood cell count increased                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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, poisoning and procedural complications  |                  |                  |                  |
| Accident at work                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Acetabulum fracture                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anaemia postoperative                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Animal bite                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ankle fracture                                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Avulsion fracture                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Back injury                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Brain contusion                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chest injury                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chemical poisoning                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| Cardiac procedure complication                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Clavicle fracture                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Concussion                                      |                  |                  |                  |

|   |                   |                  |                   |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 2 / 2345 (0.09%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Coronary artery restenosis                      |                   |                  |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%)  | 4 / 2345 (0.17%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Contusion                                       |                   |                  |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%)  | 2 / 2345 (0.09%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Craniocerebral injury                           |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Deep vein thrombosis postoperative              |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Femoral neck fracture                           |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Fall  |                   |                  |                   |
| subjects affected / exposed                     | 16 / 2333 (0.69%) | 9 / 2345 (0.38%) | 16 / 2342 (0.68%) |
| occurrences causally related to treatment / all | 0 / 16            | 1 / 9            | 0 / 16            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            | 0 / 0             |
| Facial bones fracture                           |                   |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Fibula fracture                                 |                   |                  |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Femur fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Foot fracture                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Fracture displacement                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Graft thrombosis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 anastomotic complication       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Head injury                                     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Hand fracture                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gun shot wound                                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hip fracture                                    |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Humerus fracture                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Injury  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intentional overdose                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 anastomosis complication             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Joint dislocation                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Joint injury                                    |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Kidney rupture                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Laceration                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ligament rupture                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ligament sprain                                 |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Limb injury                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meniscus injury                                 |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Multiple fractures                              |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 injuries                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Muscle injury                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Open fracture                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Overdose  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pelvic fracture                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Periorbital contusion                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 restenosis                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Periprosthetic fracture                         |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Perirenal haematoma                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Post laminectomy syndrome                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Post procedural discomfort                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Post procedural haematuria                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 haemorrhage                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Postoperative ileus                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pubis fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Radius fracture                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rib fracture                                    |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 4 / 2345 (0.17%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Road traffic accident                           |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 6 / 2345 (0.26%) | 9 / 2342 (0.38%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 2            |
| Scar  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Seroma  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 abrasion                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 column injury                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal fracture                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stab wound                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Splenic rupture                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Subdural haematoma                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Subdural haemorrhage                            |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Tendon injury                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tendon rupture                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thoracic vertebral fracture                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 injury                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 7 / 2333 (0.30%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Toxicity to various agents                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Traumatic haematoma                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Traumatic intracranial haemorrhage              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Traumatic haemorrhage                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Traumatic renal injury                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 liver injury                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ulna fracture                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Upper limb fracture                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| 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 graft occlusion                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular graft thrombosis                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Wound   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 3 / 2345 (0.13%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Wound dehiscence                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular pseudoaneurysm                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Wrist fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Congenital, familial and genetic disorders      |                  |                  |                  |
| Atrial septal defect                            |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Hydrocele                                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Congenital anomalies of ear ossicles            |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Phimosis  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Pyloric stenosis                                |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 coronary syndrome                         |                   |                   |                   |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 10 / 2345 (0.43%) | 14 / 2342 (0.60%) |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 10            | 0 / 14            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             | 0 / 1             |
| Acute myocardial infarction                     |                   |                   |                   |
| subjects affected / exposed                     | 42 / 2333 (1.80%) | 32 / 2345 (1.36%) | 48 / 2342 (2.05%) |
| occurrences causally related to treatment / all | 2 / 46            | 2 / 33            | 2 / 56            |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 3             | 0 / 6             |
| Angina pectoris                                 |                   |                   |                   |
| subjects affected / exposed                     | 32 / 2333 (1.37%) | 36 / 2345 (1.54%) | 42 / 2342 (1.79%) |
| occurrences causally related to treatment / all | 2 / 33            | 2 / 40            | 3 / 45            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Angina unstable                                 |                   |                   |                   |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 87 / 2333 (3.73%) | 82 / 2345 (3.50%) | 73 / 2342 (3.12%) |
| occurrences causally related to treatment / all | 3 / 106           | 13 / 101          | 3 / 89            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Aortic valve disease                            |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Aortic valve stenosis                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Arrhythmia                                      |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 5 / 2345 (0.21%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0             |
| Arteriosclerosis coronary artery                |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%)  | 6 / 2342 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial fibrillation                             |                   |                   |                   |
| subjects affected / exposed                     | 14 / 2333 (0.60%) | 25 / 2345 (1.07%) | 12 / 2342 (0.51%) |
| occurrences causally related to treatment / all | 0 / 14            | 1 / 27            | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial flutter                                  |                   |                   |                   |
| subjects affected / exposed                     | 5 / 2333 (0.21%)  | 7 / 2345 (0.30%)  | 4 / 2342 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 7             | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial tachycardia                              |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial thrombosis                               |                   |                   |                   |



|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Atrioventricular block                          |                   |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%)  | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Atrioventricular block complete                 |                   |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Atrioventricular block first degree             |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bradyarrhythmia                                 |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 second degree            |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bradycardia                                     |                   |                  |                  |
| subjects affected / exposed                     | 11 / 2333 (0.47%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 1 / 11            | 1 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bundle branch block bilateral                   |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bundle branch block right                       |                   |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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 arrest                                  |                   |                   |                   |
| subjects affected / exposed                     | 12 / 2333 (0.51%) | 6 / 2345 (0.26%)  | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 6             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 2             | 0 / 2             |
| Cardiac disorder                                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardiac asthma                                  |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0             |
| Cardiac failure                                 |                   |                   |                   |
| subjects affected / exposed                     | 55 / 2333 (2.36%) | 42 / 2345 (1.79%) | 24 / 2342 (1.02%) |
| occurrences causally related to treatment / all | 1 / 67            | 3 / 50            | 1 / 25            |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 3             | 0 / 1             |
| Cardiac failure acute                           |                   |                   |                   |
| subjects affected / exposed                     | 9 / 2333 (0.39%)  | 4 / 2345 (0.17%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 4             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             | 0 / 0             |
| Cardiac failure chronic                         |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 4 / 2345 (0.17%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardiac failure congestive                      |                   |                   |                   |
| subjects affected / exposed                     | 45 / 2333 (1.93%) | 30 / 2345 (1.28%) | 35 / 2342 (1.49%) |
| occurrences causally related to treatment / all | 0 / 63            | 2 / 39            | 1 / 48            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0             | 0 / 1             |
| Cardiac failure high output                     |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 6 / 2333 (0.26%) | 5 / 2345 (0.21%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 4            | 0 / 2            |
| Cardiogenic shock                               |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            | 0 / 2            |
| Cardiomyopathy                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Cardiopulmonary failure                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 1            |
| Cardiorenal syndrome                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiovascular insufficiency                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiovascular disorder                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 cardiomyopathy                       |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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                     | 46 / 2333 (1.97%) | 21 / 2345 (0.90%) | 29 / 2342 (1.24%) |
| occurrences causally related to treatment / all | 0 / 48            | 0 / 26            | 1 / 33            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0             | 0 / 0             |
| Coronary artery insufficiency                   |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Coronary artery occlusion                       |                   |                   |                   |
| subjects affected / exposed                     | 6 / 2333 (0.26%)  | 3 / 2345 (0.13%)  | 7 / 2342 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 3             | 0 / 7             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Coronary artery stenosis                        |                   |                   |                   |
| subjects affected / exposed                     | 5 / 2333 (0.21%)  | 5 / 2345 (0.21%)  | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 6             | 1 / 5             | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cyanosis  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Diastolic dysfunction                           |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Hypertensive cardiomyopathy                     |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Hypertensive heart disease                      |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Intracardiac thrombus                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ischaemic cardiomyopathy                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Left atrial dilatation                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Left ventricular dysfunction                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Left ventricular failure                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Microvascular coronary artery disease           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 15 / 2333 (0.64%) | 5 / 2345 (0.21%)  | 7 / 2342 (0.30%)  |
| occurrences causally related to treatment / all | 0 / 16            | 1 / 5             | 0 / 7             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Myocardial infarction                           |                   |                   |                   |
| subjects affected / exposed                     | 47 / 2333 (2.01%) | 50 / 2345 (2.13%) | 44 / 2342 (1.88%) |
| occurrences causally related to treatment / all | 3 / 48            | 8 / 55            | 1 / 48            |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 12            | 0 / 9             |
| Nodal arrhythmia                                |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Myocarditis                                     |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Pericardial cyst                                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Palpitations                                    |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 2 / 2345 (0.09%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Papillary muscle disorder                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Pericardial effusion                            |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 2 / 2345 (0.09%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Pericarditis                                    |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Right ventricular failure                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Postinfarction angina                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Silent myocardial infarction                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 2 / 3            | 1 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sinus arrhythmia                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.17%) | 5 / 2345 (0.21%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sinus bradycardia                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sinus node dysfunction                          |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 5 / 2345 (0.21%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tachycardia                                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Systolic dysfunction                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Tachycardia paroxysmal                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Trifascicular block                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ventricular extrasystoles                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ventricular arrhythmia                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ventricular fibrillation                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Ventricular tachycardia                         |                  |                  |                  |
| subjects affected / exposed                     | 8 / 2333 (0.34%) | 2 / 2345 (0.09%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 2            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Nervous system disorders                        |                  |                  |                  |
| Altered state of consciousness                  |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aphasia   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Amnesia   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Balance disorder                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Autonomic neuropathy                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Brain oedema                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Brain stem haemorrhage                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Brain stem infarction                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Brain stem ischaemia                            |                  |                  |                  |

|   |                   |                  |                   |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Brain stem stroke                               |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 arteriosclerosis                        |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Carotid artery occlusion                        |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 4 / 2342 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Carotid artery disease                          |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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                     | 10 / 2333 (0.43%) | 7 / 2345 (0.30%) | 12 / 2342 (0.51%) |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 7            | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Carotid artery thrombosis                       |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Carpal tunnel syndrome                          |                   |                  |                   |
| subjects affected / exposed                     | 3 / 2333 (0.13%)  | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Central nervous system inflammation             |                   |                  |                   |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebellar infarction                           |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebral arteriosclerosis                       |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 artery occlusion                       |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebral artery stenosis                        |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 ataxia                                 |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebral infarction                             |                  |                  |                   |
| subjects affected / exposed                     | 7 / 2333 (0.30%) | 7 / 2345 (0.30%) | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 7            | 1 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebral ischaemia                              |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Cerebrovascular accident                        |                  |                  |                   |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 31 / 2333 (1.33%) | 46 / 2345 (1.96%) | 37 / 2342 (1.58%) |
| occurrences causally related to treatment / all | 1 / 34            | 0 / 47            | 0 / 39            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 3             | 0 / 2             |
| Cerebrovascular disorder                        |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0             |
| Cerebrovascular insufficiency                   |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cervical cord compression                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Cervical myelopathy                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cervical radiculopathy                          |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cognitive disorder                              |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Complex partial seizures                        |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Coordination abnormal                           |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dementia Alzheimer's type                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Diabetic neuropathy                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dizziness                                       |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 8 / 2345 (0.34%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dysarthria                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Embolic cerebral infarction                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Embolic stroke                                  |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Encephalopathy                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Epilepsy  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Generalised tonic-clonic seizure                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Guillain-Barre syndrome                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Haemorrhage intracranial                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Haemorrhagic cerebral infarction                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Haemorrhagic stroke                             |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 0 / 2345 (0.00%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 0            |
| Headache  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hemiparesis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hemiplegia                                      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hydrocephalus                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypercapnic coma                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hyperkinesia                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Hypoaesthesia                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoglycaemic coma                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypotonia                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| IIIrd nerve paralysis                           |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Intercostal neuralgia                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Ischaemic cerebral infarction                   |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Ischaemic stroke                                |                   |                   |                   |
| subjects affected / exposed                     | 22 / 2333 (0.94%) | 18 / 2345 (0.77%) | 20 / 2342 (0.85%) |
| occurrences causally related to treatment / all | 1 / 26            | 1 / 18            | 1 / 24            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             | 0 / 1             |
| Lacunar infarction                              |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Leukoencephalopathy                             |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Loss of consciousness                           |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Lumbar radiculopathy                            |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Metabolic encephalopathy                        |                   |                   |                   |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Migraine  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mononeuritis                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Monoplegia                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Muscle spasticity                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myelitis transverse                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myelopathy                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myoclonus                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nerve root compression                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neuroleptic malignant syndrome                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Neuropathy peripheral                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Paraesthesia                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Paraplegia                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Paraparesis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Parkinson's disease                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Partial seizures                                |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral motor neuropathy                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Peroneal nerve palsy                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Petit mal epilepsy                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Piriformis syndrome                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Presyncope                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Radiculopathy                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sciatica  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Seizure   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 7 / 2345 (0.30%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 9            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sensory disturbance                             |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 cord compression                         |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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                     | 3 / 2333 (0.13%) | 3 / 2345 (0.13%) | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0             |
| Spondylitic myelopathy                          |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Syncope   |                  |                  |                   |
| subjects affected / exposed                     | 8 / 2333 (0.34%) | 9 / 2345 (0.38%) | 18 / 2342 (0.77%) |
| occurrences causally related to treatment / all | 0 / 8            | 2 / 9            | 1 / 19            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Subdural hygroma                                |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Thalamic infarction                             |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Thrombotic cerebral infarction                  |                  |                  |                   |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Thrombotic stroke                               |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0             |
| Transient ischaemic attack                      |                   |                   |                   |
| subjects affected / exposed                     | 23 / 2333 (0.99%) | 23 / 2345 (0.98%) | 30 / 2342 (1.28%) |
| occurrences causally related to treatment / all | 1 / 26            | 0 / 24            | 0 / 30            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| VIIth nerve paralysis                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Vascular encephalopathy                         |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Vertebral artery dissection                     |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Vertebral artery stenosis                       |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Vertebrobasilar insufficiency                   |                   |                   |                   |
| subjects affected / exposed                     | 3 / 2333 (0.13%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Vocal cord paresis                              |                   |                   |                   |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Blood and lymphatic system disorders</b>     |                   |                  |                  |
| <b>Anaemia</b>                                  |                   |                  |                  |
| subjects affected / exposed                     | 12 / 2333 (0.51%) | 8 / 2345 (0.34%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 1 / 12            | 0 / 8            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Coagulopathy</b>                             |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Febrile neutropenia</b>                      |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Haemorrhagic anaemia</b>                     |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Hypereosinophilic syndrome</b>               |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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>Hypochromic anaemia</b>                      |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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>Hypocoagulable state</b>                     |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| <b>Iron deficiency anaemia</b>                  |                   |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Microcytic anaemia                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neutropenia                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Normochromic normocytic anaemia                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombocytopenia                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ear and labyrinth disorders                     |                  |                  |                  |
| Deafness  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cerumen impaction                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Deafness unilateral                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Sudden hearing loss                             |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tinnitus  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Tympanic membrane perforation                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 7 / 2333 (0.30%) | 2 / 2345 (0.09%) | 9 / 2342 (0.38%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2            | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vertigo positional                              |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Eye disorders                                   |                  |                  |                  |
| Amaurosis                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blindness                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Blindness unilateral                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cataract  |                  |                  |                  |



|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 13 / 2345 (0.55%) | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 16            | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Cataract cortical                               |                  |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Corneal degeneration                            |                  |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Diabetic retinopathy                            |                  |                   |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Exfoliation syndrome                            |                  |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Glaucoma  |                  |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Keratopathy                                     |                  |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Macular fibrosis                                |                  |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Macular oedema                                  |                  |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Papilloedema                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 artery occlusion                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinal detachment                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinal haemorrhage                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 tear                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinoschisis                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinopathy                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Visual acuity reduced                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Vitreous haemorrhage                            |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vitreous opacities                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal disorders                      |                  |                  |                  |
| Abdominal hernia                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal pain                                  |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 5 / 2345 (0.21%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Abdominal hernia obstructive                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 pain lower                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 pain upper                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anal fissure                                    |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ascites   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bezoar  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 gastritis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colitis   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colitis ischaemic                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colon dysplasia                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Constipation                                    |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Crohn's disease                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dental caries                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 gastroparesis                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 gastropathy                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diarrhoea                                       |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 6 / 2345 (0.26%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 7            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal perforation                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diverticulum                                    |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diverticulum intestinal                         |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal ulcer haemorrhage                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal ulcer                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal ulcer perforation                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Duodenitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dysphagia                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Dyspepsia                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Enteritis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Erosive duodenitis                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Epigastric discomfort                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Food poisoning                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Faecaloma                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric haemorrhage                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 perforation                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric polyps                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric ulcer                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric ulcer haemorrhage                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastritis                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastritis erosive                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric ulcer perforation                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastritis haemorrhagic                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Gastroduodenal ulcer                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 angiodysplasia                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastroduodenitis                                |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 disorder                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal haemorrhage                    |                  |                  |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 4 / 2345 (0.17%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 4            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Gastrooesophageal reflux disease                |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 7 / 2345 (0.30%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 7            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gingival bleeding                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemorrhoidal haemorrhage                       |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemorrhoids                                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemorrhoids thrombosed                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ileus   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ileus paralytic                                 |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Impaired gastric emptying                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Incarcerated umbilical hernia                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Inguinal hernia                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 5 / 2345 (0.21%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Inguinal hernia strangulated                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intestinal haemorrhage                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.09%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Intestinal obstruction                          |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 1 / 2345 (0.04%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Irritable bowel syndrome                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 perforation                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Large intestinal ulcer                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large intestine polyp                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 5 / 2345 (0.21%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large intestine perforation                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 intraabdominal fluid collection       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lumbar hernia                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mallory-Weiss syndrome                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Melaena   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nausea  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 4 / 2345 (0.17%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mesenteric vein thrombosis                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 stenosis                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oesophagitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 3 / 2345 (0.13%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatitis acute                              |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 2 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatitis chronic                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 relapsing                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Peptic ulcer                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peptic ulcer haemorrhage                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Peptic ulcer perforation                        |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peritoneal haemorrhage                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Rectal haemorrhage                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small intestinal obstruction                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 3 / 2345 (0.13%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stomatitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small intestinal perforation                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Subileus  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stress ulcer                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Upper gastrointestinal haemorrhage              |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| Umbilical hernia                                |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombosis mesenteric vessel                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Varices oesophageal                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Volvulus  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Vomiting  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 3 / 2345 (0.13%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Skin and subcutaneous tissue disorders          |                  |                  |                  |
| Angioedema                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cold sweat                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dermal cyst                                     |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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>Dermatitis contact</b>                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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>Diabetic bullosis</b>                        |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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>Diabetic foot</b>                            |                   |                   |                   |
| subjects affected / exposed                     | 12 / 2333 (0.51%) | 10 / 2345 (0.43%) | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 10            | 0 / 14            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| <b>Eczema</b>                                   |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| <b>Erythema</b>                                 |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| <b>Erythrodermic psoriasis</b>                  |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| <b>Ingrowing nail</b>                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| <b>Leukoplakia</b>                              |                   |                   |                   |



|   |                   |                  |                   |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Neuropathic ulcer                               |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Pemphigus                                       |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Skin fibrosis                                   |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 necrosis                                   |                   |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            | 0 / 0             |
| Skin ulcer                                      |                   |                  |                   |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 6 / 2345 (0.26%) | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 7            | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            | 0 / 0             |
| Skin ulcer haemorrhage                          |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0             |
| Urticaria                                       |                   |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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 and urinary disorders                     |                   |                  |                   |
| Acute kidney injury                             |                   |                  |                   |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 32 / 2333 (1.37%) | 26 / 2345 (1.11%) | 19 / 2342 (0.81%) |
| occurrences causally related to treatment / all | 3 / 34            | 0 / 27            | 4 / 19            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Acute prerenal failure                          |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Albuminuria                                     |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 neck sclerosis                          |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Anuria  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Bladder outlet obstruction                      |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Calculus bladder                                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Calculus ureteric                               |                   |                   |                   |
| subjects affected / exposed                     | 4 / 2333 (0.17%)  | 1 / 2345 (0.04%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Calculus urinary                                |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cystitis glandularis                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chronic kidney disease                          |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cystitis haemorrhagic                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dysuria   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haematuria                                      |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hydronephrosis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypertensive nephropathy                        |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Lower urinary tract symptoms                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Microalbuminuria                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nephritis                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nephrolithiasis                                 |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 3 / 2345 (0.13%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nephropathy                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nephrotic syndrome                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Obstructive uropathy                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oliguria  |                  |                  |                  |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Polyuria  |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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 artery arteriosclerosis                   |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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 artery stenosis                           |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Renal colic                                     |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Renal cyst                                      |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 impairment                                |                   |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Renal failure                                   |                   |                  |                  |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 2            | 1 / 4            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            | 0 / 0            |
| Renal tubular necrosis                          |                   |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 infarct                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stress urinary incontinence                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 obstruction                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urethral stenosis                               |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 4 / 2345 (0.17%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary bladder haemorrhage                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary bladder polyp                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Urinary incontinence                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Urinary retention                               |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 4 / 2345 (0.17%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary tract obstruction                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endocrine disorders                             |                  |                  |                  |
| Basedow's disease                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Goitre  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperparathyroidism                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperparathyroidism primary                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Musculoskeletal and connective tissue disorders |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Arthralgia                                      |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 1 / 2345 (0.04%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arthritis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Back pain                                       |                  |                  |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 3 / 2345 (0.13%) | 8 / 2342 (0.34%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 3            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bursitis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bone fistula                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cervical spinal stenosis                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Costochondritis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dupuytren's contracture                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dactylitis                                      |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Foot deformity                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Flank pain                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fistula   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fracture nonunion                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fracture delayed union                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gouty arthritis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gouty tophus                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 compression                 |                  |                  |                  |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Intervertebral disc degeneration                |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Intervertebral disc protrusion                  |                   |                  |                  |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 4 / 2345 (0.17%) | 6 / 2342 (0.26%) |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 4            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Intervertebral disc disorder                    |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Lumbar spinal stenosis                          |                   |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Lower extremity mass                            |                   |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Muscle tightness                                |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Muscle twitching                                |                   |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Muscular weakness                               |                   |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Musculoskeletal chest pain                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Musculoskeletal pain                            |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Musculoskeletal disorder                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Myofascial pain syndrome                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myalgia   |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myositis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neck pain                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neuropathic arthropathy                         |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 2 / 2345 (0.09%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Osteitis  |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 deformans                              |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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                     | 15 / 2333 (0.64%) | 15 / 2345 (0.64%) | 17 / 2342 (0.73%) |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 16            | 0 / 18            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Osteomalacia                                    |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Osteonecrosis                                   |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Osteoporosis                                    |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Osteoporotic fracture                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Pain in extremity                               |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 3 / 2345 (0.13%) | 6 / 2342 (0.26%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pathological fracture                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Periarthritis                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rhabdomyolysis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rotator cuff syndrome                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 6 / 2345 (0.26%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal column stenosis                          |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal osteoarthritis                           |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal pain                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spondylitis                                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Spondylolisthesis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Synovitis                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tendonitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Tenosynovitis stenosans                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Trigger finger                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infections and infestations                     |                  |                  |                  |
| Abdominal abscess                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal wall abscess                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abscess   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abscess limb                                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 6 / 2345 (0.26%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abscess of eyelid                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 sinusitis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Amoebiasis                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Amoebic dysentery                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anal abscess                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Appendicitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 5 / 2345 (0.21%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Appendicitis perforated                         |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arteriosclerotic gangrene                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arthritis bacterial                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Atypical pneumonia                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bacteraemia                                     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bacterial sepsis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Biliary tract infection                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Bone abscess                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Bronchiolitis                                   |                  |                  |                  |



|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Bronchitis                                      |                   |                   |                   |
| subjects affected / exposed                     | 10 / 2333 (0.43%) | 5 / 2345 (0.21%)  | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 5             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Bronchitis viral                                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Bronchopneumonia                                |                   |                   |                   |
| subjects affected / exposed                     | 3 / 2333 (0.13%)  | 1 / 2345 (0.04%)  | 3 / 2342 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Catheter site infection                         |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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                     | 20 / 2333 (0.86%) | 11 / 2345 (0.47%) | 17 / 2342 (0.73%) |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 20            | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0             | 0 / 0             |
| Cellulitis gangrenous                           |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 2 / 2345 (0.09%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cellulitis of male external genital organ       |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cellulitis staphylococcal                       |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholecystitis infective                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 sinusitis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Clostridium difficile colitis                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cutaneous larva migrans                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cystitis bacterial                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Dengue fever                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device related infection                        |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 infection                         |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 5 / 2345 (0.21%) | 7 / 2342 (0.30%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 6            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device related sepsis                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Diverticulitis                                  |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 3 / 2345 (0.13%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic gangrene                               |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Eczema infected                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Ear infection                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endocarditis                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Empyema   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 infectious                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 viral                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endophthalmitis                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Erysipelas                                      |                  |                  |                  |
| subjects affected / exposed                     | 9 / 2333 (0.39%) | 8 / 2345 (0.34%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 8            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Escherichia urinary tract infection             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Escherichia sepsis                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Furuncle  |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 infection                               |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Gastroenteritis                                 |                   |                   |                   |
| subjects affected / exposed                     | 15 / 2333 (0.64%) | 18 / 2345 (0.77%) | 15 / 2342 (0.64%) |
| occurrences causally related to treatment / all | 0 / 16            | 1 / 18            | 2 / 17            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Gallbladder empyema                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Gangrene  |                   |                   |                   |
| subjects affected / exposed                     | 8 / 2333 (0.34%)  | 10 / 2345 (0.43%) | 6 / 2342 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 13            | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Gastroenteritis salmonella                      |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| 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 viral                           |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Gastrointestinal infection                      |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Gastrointestinal protozoal infection            |                   |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Giardiasis                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| H1N1 influenza                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infected skin ulcer                             |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Infectious colitis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Incision site infection                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infectious pleural effusion                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Influenza                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Inguinal hernia gangrenous                      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infusion site infection                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intestinal fistula infection                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 tuberculosis                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Kidney infection                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Klebsiella infection                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Labyrinthitis                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Liver abscess                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lobar pneumonia                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Localised infection                             |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 2 / 2345 (0.09%) | 4 / 2342 (0.17%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lower respiratory tract infection               |                  |                  |                  |
| subjects affected / exposed                     | 4 / 2333 (0.17%) | 8 / 2345 (0.34%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 9            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lower respiratory tract infection bacterial     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Lung infection                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lyme disease                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mediastinitis                                   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meningitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Meningitis bacterial                            |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meningitis streptococcal                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Meningitis tuberculous                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Muscle abscess                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myelitis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nasal abscess                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oesophageal candidiasis                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteomyelitis acute                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteomyelitis                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 5 / 2345 (0.21%) | 9 / 2342 (0.38%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 6            | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteomyelitis bacterial                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Otitis externa                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Otitis media                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Peritonitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Periodontitis                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Peritonsillar abscess                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pertussis                                       |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Pharyngotonsillitis                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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                                       |                   |                   |                   |
| subjects affected / exposed                     | 53 / 2333 (2.27%) | 41 / 2345 (1.75%) | 38 / 2342 (1.62%) |
| occurrences causally related to treatment / all | 0 / 63            | 0 / 45            | 0 / 41            |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 3             | 0 / 3             |
| Pneumonia bacterial                             |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Pneumonia fungal                                |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 influenzal                            |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Pneumonia haemophilus                           |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 pneumococcal                          |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Postoperative wound infection                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Post procedural sepsis                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Pseudomonal sepsis                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Prostatic abscess                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 mycosis                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Psoas abscess                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyelonephritis acute                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 4 / 2345 (0.17%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 1 / 6            | 1 / 4            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyelonephritis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Respiratory tract infection                     |                  |                  |                  |
| subjects affected / exposed                     | 7 / 2333 (0.30%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Pyelonephritis chronic                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Rotavirus infection                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rhinitis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sepsis  |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 7 / 2345 (0.30%) | 6 / 2342 (0.26%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            | 1 / 6            |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3            | 0 / 1            |
| Scrotal abscess                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Septic encephalopathy                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Septic shock                                    |                  |                  |                  |
| subjects affected / exposed                     | 8 / 2333 (0.34%) | 2 / 2345 (0.09%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2            | 1 / 5            |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2            | 1 / 1            |
| Sinusitis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 infection                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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            |
| Staphylococcal skin infection                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Staphylococcal sepsis                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| 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 infection                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Subcutaneous abscess                            |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Tonsillitis                                     |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Tuberculosis                                    |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Tracheobronchitis                               |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 2 / 2345 (0.09%)  | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Tuberculous pleurisy                            |                   |                   |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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             |
| Upper respiratory tract infection               |                   |                   |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%)  | 1 / 2345 (0.04%)  | 2 / 2342 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Urinary tract infection pseudomonal             |                   |                   |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Urinary tract infection                         |                   |                   |                   |
| subjects affected / exposed                     | 16 / 2333 (0.69%) | 13 / 2345 (0.55%) | 16 / 2342 (0.68%) |
| occurrences causally related to treatment / all | 4 / 16            | 6 / 14            | 3 / 16            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Urinary tract infection fungal                  |                   |                   |                   |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 3 / 2342 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Urosepsis                                       |                  |                  |                   |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 6 / 2345 (0.26%) | 11 / 2342 (0.47%) |
| occurrences causally related to treatment / all | 0 / 3            | 2 / 6            | 4 / 12            |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            | 1 / 1             |
| Vaginal cellulitis                              |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Vestibular neuronitis                           |                  |                  |                   |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Varicella                                       |                  |                  |                   |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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             |
| Viral infection                                 |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 2 / 2345 (0.09%) | 5 / 2342 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Wound infection                                 |                  |                  |                   |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 4 / 2345 (0.17%) | 3 / 2342 (0.13%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Wound sepsis                                    |                  |                  |                   |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%)  |
| 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              |                  |                  |                   |
| Decreased appetite                              |                  |                  |                   |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dehydration                                     |                  |                  |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%) | 5 / 2345 (0.21%) | 5 / 2342 (0.21%) |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 5            | 1 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetes mellitus                               |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 3 / 2345 (0.13%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Diabetes mellitus inadequate control            |                  |                  |                  |
| subjects affected / exposed                     | 6 / 2333 (0.26%) | 8 / 2345 (0.34%) | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 8            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic complication                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic ketoacidosis                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 3 / 2345 (0.13%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic metabolic decompensation               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fluid overload                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 0 / 2333 (0.00%)  | 0 / 2345 (0.00%)  | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Hyperglycaemia                                  |                   |                   |                  |
| subjects affected / exposed                     | 14 / 2333 (0.60%) | 5 / 2345 (0.21%)  | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 1 / 15            | 0 / 5             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Hyperkalaemia                                   |                   |                   |                  |
| subjects affected / exposed                     | 5 / 2333 (0.21%)  | 2 / 2345 (0.09%)  | 3 / 2342 (0.13%) |
| occurrences causally related to treatment / all | 1 / 5             | 0 / 2             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Hypernatraemia                                  |                   |                   |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0            |
| Hypoglycaemia                                   |                   |                   |                  |
| subjects affected / exposed                     | 17 / 2333 (0.73%) | 10 / 2345 (0.43%) | 9 / 2342 (0.38%) |
| occurrences causally related to treatment / all | 0 / 21            | 4 / 11            | 2 / 9            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Hypomagnesaemia                                 |                   |                   |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%)  | 1 / 2345 (0.04%)  | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Hypokalaemia                                    |                   |                   |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%)  | 0 / 2345 (0.00%)  | 0 / 2342 (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            |
| Hyponatraemia                                   |                   |                   |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 2 / 2345 (0.09%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypovolaemia                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Insulin resistance                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 0 / 2342 (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                     | 0 / 2333 (0.00%) | 1 / 2345 (0.04%) | 0 / 2342 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Metabolic acidosis                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 2333 (0.04%) | 0 / 2345 (0.00%) | 2 / 2342 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lipomatosis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 2333 (0.00%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Obesity   |                  |                  |                  |
| subjects affected / exposed                     | 3 / 2333 (0.13%) | 2 / 2345 (0.09%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Type 2 diabetes mellitus                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 2333 (0.09%) | 0 / 2345 (0.00%) | 1 / 2342 (0.04%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| <b>Serious adverse events</b>      | All Empagliflozin |  |  |
| Total subjects affected by serious |                   |  |  |

|   |                         |  |  |
|---|-------------------------|--|--|
| adverse events  |                         |  |  |
| subjects affected / exposed   | 1789 / 4687<br>(38.17%) |  |  |
| number of deaths (all causes)                                       | 176                     |  |  |
| number of deaths resulting from adverse events                      | 4                       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |  |  |
| Acoustic neuroma  |                         |  |  |
| subjects affected / exposed   | 3 / 4687 (0.06%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 3                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                   |  |  |
| Acute lymphocytic leukaemia   |                         |  |  |
| subjects affected / exposed   | 1 / 4687 (0.02%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                   |  |  |
| deaths causally related to treatment / all                          | 0 / 1                   |  |  |
| Acute myeloid leukaemia   |                         |  |  |
| subjects affected / exposed   | 1 / 4687 (0.02%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                   |  |  |
| deaths causally related to treatment / all                          | 0 / 1                   |  |  |
| Adenocarcinoma  |                         |  |  |
| subjects affected / exposed   | 1 / 4687 (0.02%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                   |  |  |
| deaths causally related to treatment / all                          | 0 / 1                   |  |  |
| Adenocarcinoma gastric  |                         |  |  |
| subjects affected / exposed   | 1 / 4687 (0.02%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                   |  |  |
| Adenocarcinoma of colon   |                         |  |  |
| subjects affected / exposed   | 4 / 4687 (0.09%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 4                   |  |  |
| deaths causally related to treatment / all                          | 0 / 1                   |  |  |
| Adenocarcinoma pancreas   |                         |  |  |
| subjects affected / exposed   | 6 / 4687 (0.13%)        |  |  |
| occurrences causally related to treatment / all                     | 0 / 6                   |  |  |
| deaths causally related to treatment / all                          | 0 / 4                   |  |  |
| Adenoma benign  |                         |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anogenital warts                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| B-cell lymphoma                                 |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Basal cell carcinoma                            |                   |  |  |
| subjects affected / exposed                     | 27 / 4687 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 29            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Basosquamous carcinoma                          |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Benign hepatic neoplasm                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Benign laryngeal neoplasm                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Benign lung neoplasm                            |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Benign neoplasm of adrenal gland                |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign neoplasm of bladder                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign neoplasm of prostate                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign neoplasm of thyroid gland                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign pancreatic neoplasm                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign respiratory tract neoplasm               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Benign uterine neoplasm                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bile duct cancer                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bladder cancer                                  |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |  |
| Bladder cancer recurrent                        |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bladder transitional cell carcinoma             |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bone cancer                                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bone giant cell tumour benign                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bowen's disease                                 |                  |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Brain neoplasm                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Breast cancer                                   |                  |  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bronchial carcinoma                             |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac myxoma                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cervix carcinoma                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholesteatoma                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chronic lymphocytic leukaemia                   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clear cell renal cell carcinoma                 |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colon adenoma                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colon cancer                                    |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Colon cancer metastatic                         |                  |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Colon neoplasm                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colorectal adenocarcinoma                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colorectal cancer                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endometrial cancer                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Fibroadenoma of breast                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Fibrosarcoma                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Follicular thyroid cancer                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric cancer                                  |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal stromal tumour                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Genital neoplasm malignant female               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemangioma of bone                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemangioma of liver                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic neoplasm                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatocellular carcinoma                        |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Hodgkin's disease stage I                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intraductal proliferative breast lesion         |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Invasive ductal breast carcinoma                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Keratoacanthoma                                 |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large cell lung cancer                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Laryngeal cancer                                |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Laryngeal squamous cell carcinoma               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Lipoma  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung adenocarcinoma                             |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |
| Lung cancer metastatic                          |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Lung carcinoma cell type unspecified stage III  |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lung neoplasm malignant                         |                  |  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |  |
| deaths causally related to treatment / all      | 0 / 4            |  |  |  |
| Lung squamous cell carcinoma stage III          |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lymphocytic lymphoma                            |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lymphoma  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Lymphoproliferative disorder                    |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Malignant melanoma                              |                  |  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Malignant melanoma in situ                      |                  |  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Malignant neoplasm of unknown primary site      |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Meningioma                                      |                   |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Malignant neoplasm progression                  |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Metastases to bone                              |                   |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Metastases to liver                             |                   |  |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |  |
| Metastases to lung                              |                   |  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |  |
| Metastases to lymph nodes                       |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Metastases to peritoneum                        |                   |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Metastases to neck                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metastases to pleura                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metastasis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Metastatic malignant melanoma                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myelodysplastic syndrome                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metastatic renal cell carcinoma                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuroendocrine carcinoma                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nasopharyngeal cancer                           |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |  |
| Non-Hodgkin's lymphoma stage IV                 |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Neuroendocrine carcinoma of the skin            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Non-Hodgkin's lymphoma                          |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Oesophageal adenocarcinoma                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Oesophageal carcinoma                           |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| POEMS syndrome                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pancreatic carcinoma                            |                  |  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |  |
| deaths causally related to treatment / all      | 1 / 3            |  |  |  |
| Papillary serous endometrial carcinoma          |                  |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Papillary thyroid cancer                        |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Parathyroid tumour benign                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pituitary tumour benign                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Penile squamous cell carcinoma                  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Plasma cell myeloma                             |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Prostate cancer                                 |                   |  |  |
| subjects affected / exposed                     | 20 / 4687 (0.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 20            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rectal adenocarcinoma                           |                   |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |
| Prostate cancer recurrent                       |                   |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Prostatic adenoma                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal cancer                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cancer                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cell carcinoma                            |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cancer metastatic                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cell carcinoma stage I                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cell carcinoma stage II                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Salivary gland neoplasm                         |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Salivary gland adenoma                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin cancer                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small cell carcinoma                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sarcoma   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Splenic marginal zone lymphoma                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small cell lung cancer                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Squamous cell carcinoma                         |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Squamous cell carcinoma of lung                 |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 3            |  |  |  |
| Squamous cell carcinoma of skin                 |                  |  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Squamous cell carcinoma of the oral cavity      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Thyroid neoplasm                                |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Tongue neoplasm malignant stage unspecified     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Transitional cell carcinoma                     |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Tumour haemorrhage                              |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Uterine cancer                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Uterine leiomyoma                               |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular disorders                              |                  |  |  |
| Accelerated hypertension                        |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aneurysm  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Angiopathy                                      |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aortic aneurysm                                 |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aortic arteriosclerosis                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aortic dissection                               |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aortic stenosis                                 |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Arterial disorder                               |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arterial haemorrhage                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arterial occlusive disease                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arterial stenosis                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arteriosclerosis                                |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arteriovenous fistula                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arteritis                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Deep vein thrombosis                            |                   |  |  |
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic microangiopathy                        |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Embolism  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Embolism arterial                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Extremity necrosis                              |                   |  |  |
| subjects affected / exposed                     | 12 / 4687 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Femoral artery embolism                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Femoral artery occlusion                        |                   |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Haematoma                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Haemorrhage                                     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypertension                                    |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypertensive crisis                             |                   |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypotension                                     |                   |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypertensive emergency                          |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypovolaemic shock                              |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Iliac artery occlusion                          |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Infarction                                      |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intermittent claudication                       |                   |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ischaemia                                       |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Leriche syndrome                                |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Malignant hypertension                          |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Orthostatic hypotension                         |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral arterial occlusive disease           |                   |  |  |
| subjects affected / exposed                     | 58 / 4687 (1.24%) |  |  |
| occurrences causally related to treatment / all | 1 / 75            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral artery aneurysm                      |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral artery stenosis                      |                   |  |  |
| subjects affected / exposed                     | 12 / 4687 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral artery thrombosis                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral coldness                             |                   |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral embolism                             |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral ischaemia                            |                   |  |  |
| subjects affected / exposed                     | 15 / 4687 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 16            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral vascular disorder                    |                   |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%)  |  |  |
| occurrences causally related to treatment / all | 1 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peripheral venous disease                       |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Subclavian artery stenosis                      |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombophlebitis                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombophlebitis superficial                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombosis                                      |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Varicose ulceration                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Varicose vein                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular calcification                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular insufficiency                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Venous occlusion                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Venous thrombosis                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Venous thrombosis limb                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Surgical and medical procedures                 |                  |  |  |
| Angioplasty                                     |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary angioplasty                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary arterial stent insertion               |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary artery bypass                          |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary revascularisation                      |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Fracture treatment                              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Percutaneous coronary intervention              |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Prophylaxis                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stent placement                                 |                  |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                          | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 3             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Adverse drug reaction                                |                   |  |  |
| subjects affected / exposed                          | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Cardiac death  |                   |  |  |
| subjects affected / exposed                          | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 6             |  |  |
| deaths causally related to treatment / all           | 0 / 6             |  |  |
| Asthenia   |                   |  |  |
| subjects affected / exposed                          | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 3             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Chills   |                   |  |  |
| subjects affected / exposed                          | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 0             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Chest pain   |                   |  |  |
| subjects affected / exposed                          | 65 / 4687 (1.39%) |  |  |
| occurrences causally related to treatment / all      | 1 / 68            |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Chest discomfort                                     |                   |  |  |
| subjects affected / exposed                          | 5 / 4687 (0.11%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 5             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Death  |                   |  |  |
| subjects affected / exposed                          | 15 / 4687 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 15            |  |  |
| deaths causally related to treatment / all           | 0 / 15            |  |  |
| Device defective                                     |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Device difficult to use                         |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Device deposit issue                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Device occlusion                                |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Device malfunction                              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dysplasia                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Drug ineffective                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Drowning  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Extravasation                                   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Fatigue</b>                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Gait disturbance</b>                         |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Feeling abnormal</b>                         |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Generalised oedema</b>                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>General physical health deterioration</b>    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Granuloma</b>                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Hernia</b>                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Impaired healing</b>                         |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Implant site necrosis                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Multi-organ failure                             |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Malaise   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Oedema peripheral                               |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Non-cardiac chest pain                          |                   |  |  |
| subjects affected / exposed                     | 20 / 4687 (0.43%) |  |  |
| occurrences causally related to treatment / all | 1 / 20            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Necrobiosis                                     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Oversensing                                     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pacemaker generated arrhythmia                  |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Perforated ulcer                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pain  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral swelling                             |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Polyp   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyrexia   |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stent malfunction                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Strangulated hernia                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sudden death                                    |                  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 13            |  |  |
| deaths causally related to treatment / all      | 1 / 13            |  |  |
| Sudden cardiac death                            |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Systemic inflammatory response syndrome         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ulcer   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Immune system disorders                         |                   |  |  |
| Anaphylactic reaction                           |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anaphylactic shock                              |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Food allergy                                    |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Contrast media allergy                          |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypersensitivity                                |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Iodine allergy                                  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Social circumstances                            |                   |  |  |
| Physical assault                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Reproductive system and breast disorders        |                   |  |  |
| Benign prostatic hyperplasia                    |                   |  |  |
| subjects affected / exposed                     | 18 / 4687 (0.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cystocele                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Endometrial hyperplasia                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Fibrocystic breast disease                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Genital prolapse                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| Gynaecomastia                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Menorrhagia                                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Ovarian cyst                                    |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Prostatism                                      |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Prostatic obstruction                           |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Prostatitis                                     |                  |  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Uterine polyp                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Uterine prolapse                                |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Uterovaginal prolapse                           |                  |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vaginal prolapse                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Acute pulmonary oedema                          |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Acute respiratory distress syndrome             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Acute respiratory failure                       |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Allergic sinusitis                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Asthma  |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atelectasis                                     |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bronchial disorder                              |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchial secretion retention                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchiectasis                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchitis chronic                              |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchospasm                                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Chronic obstructive pulmonary disease           |                   |  |  |
| subjects affected / exposed                     | 16 / 4687 (0.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 21            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dyspnoea  |                   |  |  |
| subjects affected / exposed                     | 15 / 4687 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 16            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dyspnoea exertional                             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Emphysema                                       |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Epistaxis                                       |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemoptysis                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemothorax                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydrothorax                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoxia   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Idiopathic pulmonary fibrosis                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Interstitial lung disease                       |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Laryngeal oedema                                |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung disorder                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung infiltration                               |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mediastinal haematoma                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nasal polyps                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Obstructive airways disorder                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paranasal cyst                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleural effusion                                |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleural fibrosis                                |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pleurisy  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleuritic pain                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia aspiration                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonitis                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumothorax                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pulmonary arterial hypertension                 |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary congestion                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary embolism                              |                  |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pulmonary fibrosis                              |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 2            |  |  |
| Pulmonary hypertension                          |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary mass                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary oedema                                |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary thrombosis                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary toxicity                              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory distress                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory arrest                              |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory failure                             |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinus disorder                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sleep apnoea syndrome                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Status asthmaticus                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper airway obstruction                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vocal cord polyp                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vocal cord thickening                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Anxiety   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Completed suicide                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Confusional state                               |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Delirium  |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Depression                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hallucination                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Insomnia  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Major depression                                |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mental status changes                           |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rapid eye movements sleep abnormal              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Substance abuse                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Suicidal ideation                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Suicide attempt                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Bile duct obstruction                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bile duct stone                                 |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholecystitis                                   |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholecystitis acute                             |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cholangitis                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cholelithiasis                                  |                   |  |  |
| subjects affected / exposed                     | 21 / 4687 (0.45%) |  |  |
| occurrences causally related to treatment / all | 1 / 21            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cholecystitis chronic                           |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gallbladder disorder                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cholestasis                                     |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatic cirrhosis                               |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatic failure                                 |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatic steatosis                               |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ischaemic hepatitis                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic function abnormal                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Non-alcoholic steatohepatitis                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jaundice cholestatic                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Portal hypertension                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post cholecystectomy syndrome                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sphincter of Oddi dysfunction                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Investigations                                  |                  |  |  |
| Alanine aminotransferase increased              |                  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Angiogram normal                                |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Angiogram                                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Arteriogram coronary                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Anticoagulation drug level above therapeutic    |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood calcium decreased                         |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Aspartate aminotransferase increased            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Biopsy lung                                     |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood creatine phosphokinase MB increased       |                  |  |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood creatine phosphokinase increased          |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood glucose fluctuation                       |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood creatinine increased                      |                  |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood lactate dehydrogenase increased           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood magnesium decreased                       |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood potassium increased                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood pressure increased                        |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Blood urea increased                            |                  |  |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood pressure orthostatic decreased            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac murmur                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| C-reactive protein increased                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac stress test abnormal                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Catheterisation cardiac                         |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ejection fraction decreased                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Electrocardiogram T wave inversion              |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemoglobin decreased                           |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic enzyme increased                        |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Heart rate irregular                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lipase increased                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Liver function test abnormal                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oxygen consumption increased                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Physical examination                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Prostatic specific antigen increased            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Scan myocardial perfusion abnormal              |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Smear cervix abnormal                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Transaminases increased                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Troponin I increased                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Troponin increased                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Weight decreased                                |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| White blood cell count increased                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury, poisoning and procedural complications  |                  |  |  |
| Accident at work                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Acetabulum fracture                             |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anaemia postoperative                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Animal bite                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ankle fracture                                  |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Avulsion fracture                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Back injury                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain contusion                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chest injury                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chemical poisoning                              |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cardiac procedure complication                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clavicle fracture                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Concussion                                      |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Coronary artery restenosis                      |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Contusion                                       |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Craniocerebral injury                           |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Deep vein thrombosis postoperative              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Femoral neck fracture                           |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Fall  |                   |  |  |
| subjects affected / exposed                     | 25 / 4687 (0.53%) |  |  |
| occurrences causally related to treatment / all | 1 / 25            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Facial bones fracture                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Fibula fracture                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Femur fracture                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Foot fracture                                   |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Fracture displacement                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Graft thrombosis                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal anastomotic complication       |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Head injury                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Hand fracture                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gun shot wound                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hip fracture                                    |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Humerus fracture                                |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Incisional hernia                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intentional overdose                            |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal anastomosis complication             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Joint dislocation                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Joint injury                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Kidney rupture                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Laceration                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ligament rupture                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ligament sprain                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Limb injury                                     |                  |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Meniscus injury                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Multiple fractures                              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Multiple injuries                               |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscle injury                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Open fracture                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Overdose  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pelvic fracture                                 |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Periorbital contusion                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral artery restenosis                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Periprosthetic fracture                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Perirenal haematoma                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post laminectomy syndrome                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural discomfort                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural haematuria                      |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural haemorrhage                     |                  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Postoperative ileus                             |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pubis fracture                                  |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Radius fracture                                 |                   |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Rib fracture                                    |                   |  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 8             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Road traffic accident                           |                   |  |  |  |
| subjects affected / exposed                     | 15 / 4687 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 15            |  |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |  |
| Scar  |                   |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Seroma  |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Skin abrasion                                   |                   |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal column injury                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal fracture                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal compression fracture                     |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stab wound                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Splenic rupture                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subdural haematoma                              |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subdural haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tendon injury                                   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tendon rupture                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thoracic vertebral fracture                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tongue injury                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tibia fracture                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Toxicity to various agents                      |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic haematoma                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic intracranial haemorrhage              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic haemorrhage                           |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic renal injury                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Traumatic liver injury                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ulna fracture                                   |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular graft occlusion                        |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular graft thrombosis                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wound   |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wound dehiscence                                |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular pseudoaneurysm                         |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wrist fracture                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Congenital, familial and genetic disorders      |                  |  |  |
| Atrial septal defect                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydrocele                                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Congenital anomalies of ear ossicles            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Phimosis  |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyloric stenosis                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac disorders                               |                  |  |  |

|   |                    |  |  |  |
|---|--------------------|--|--|--|
| Acute coronary syndrome                         |                    |  |  |  |
| subjects affected / exposed                     | 24 / 4687 (0.51%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 24             |  |  |  |
| deaths causally related to treatment / all      | 0 / 1              |  |  |  |
| Acute myocardial infarction                     |                    |  |  |  |
| subjects affected / exposed                     | 80 / 4687 (1.71%)  |  |  |  |
| occurrences causally related to treatment / all | 4 / 89             |  |  |  |
| deaths causally related to treatment / all      | 0 / 9              |  |  |  |
| Angina pectoris                                 |                    |  |  |  |
| subjects affected / exposed                     | 78 / 4687 (1.66%)  |  |  |  |
| occurrences causally related to treatment / all | 5 / 85             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Angina unstable                                 |                    |  |  |  |
| subjects affected / exposed                     | 155 / 4687 (3.31%) |  |  |  |
| occurrences causally related to treatment / all | 16 / 190           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Aortic valve disease                            |                    |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 2              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Aortic valve stenosis                           |                    |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 2              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Arrhythmia                                      |                    |  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 6              |  |  |  |
| deaths causally related to treatment / all      | 0 / 1              |  |  |  |
| Arteriosclerosis coronary artery                |                    |  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 7              |  |  |  |
| deaths causally related to treatment / all      | 0 / 0              |  |  |  |
| Atrial fibrillation                             |                    |  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 37 / 4687 (0.79%) |  |  |
| occurrences causally related to treatment / all | 1 / 40            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrial flutter                                  |                   |  |  |
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrial tachycardia                              |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrial thrombosis                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrioventricular block                          |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrioventricular block complete                 |                   |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrioventricular block first degree             |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bradyarrhythmia                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrioventricular block second degree            |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bradycardia                                     |                   |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 1 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bundle branch block bilateral                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bundle branch block right                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiac arrest                                  |                   |  |  |
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Cardiac disorder                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiac asthma                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cardiac failure                                 |                   |  |  |
| subjects affected / exposed                     | 66 / 4687 (1.41%) |  |  |
| occurrences causally related to treatment / all | 4 / 75            |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Cardiac failure acute                           |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cardiac failure chronic                         |                   |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiac failure congestive                      |                   |  |  |
| subjects affected / exposed                     | 65 / 4687 (1.39%) |  |  |
| occurrences causally related to treatment / all | 3 / 87            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cardiac failure high output                     |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardio-respiratory arrest                       |                   |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 6             |  |  |
| Cardiogenic shock                               |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Cardiomyopathy                                  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiopulmonary failure                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cardiorenal syndrome                            |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiovascular insufficiency                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiovascular disorder                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Congestive cardiomyopathy                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coronary artery disease                         |                   |  |  |
| subjects affected / exposed                     | 50 / 4687 (1.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 59            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coronary artery insufficiency                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coronary artery occlusion                       |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coronary artery stenosis                        |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 1 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cyanosis  |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diastolic dysfunction                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypertensive cardiomyopathy                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypertensive heart disease                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Intracardiac thrombus                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ischaemic cardiomyopathy                        |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Left atrial dilatation                          |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Left ventricular dysfunction                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Left ventricular failure                        |                  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Microvascular coronary artery disease           |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Mitral valve incompetence                       |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Myocardial ischaemia                            |                   |  |  |  |
| subjects affected / exposed                     | 12 / 4687 (0.26%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 12            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Myocardial infarction                           |                   |  |  |  |
| subjects affected / exposed                     | 94 / 4687 (2.01%) |  |  |  |
| occurrences causally related to treatment / all | 9 / 103           |  |  |  |
| deaths causally related to treatment / all      | 0 / 21            |  |  |  |
| Nodal arrhythmia                                |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Myocarditis                                     |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pericardial cyst                                |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Palpitations                                    |                   |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Papillary muscle disorder                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pericardial effusion                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pericarditis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Right ventricular failure                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Postinfarction angina                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Silent myocardial infarction                    |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 3 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinus arrhythmia                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Supraventricular tachycardia                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinus bradycardia                               |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinus node dysfunction                          |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tachycardia                                     |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Systolic dysfunction                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tachycardia paroxysmal                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Trifascicular block                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ventricular extrasystoles                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ventricular arrhythmia                          |                  |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ventricular fibrillation                        |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Ventricular tachycardia                         |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorders                        |                  |  |  |
| Altered state of consciousness                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aphasia   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Amnesia   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Balance disorder                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Autonomic neuropathy                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain oedema                                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain stem haemorrhage                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Brain stem infarction                           |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain stem ischaemia                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Brain stem stroke                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Carotid arteriosclerosis                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Carotid artery occlusion                        |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Carotid artery disease                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Carotid artery stenosis                         |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 19 / 4687 (0.41%) |  |  |
| occurrences causally related to treatment / all | 0 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Carotid artery thrombosis                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Carpal tunnel syndrome                          |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Central nervous system inflammation             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebellar infarction                           |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral arteriosclerosis                       |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral artery occlusion                       |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral artery stenosis                        |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral ataxia                                 |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral infarction                             |                   |  |  |
| subjects affected / exposed                     | 18 / 4687 (0.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 18            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebral ischaemia                              |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerebrovascular accident                        |                   |  |  |
| subjects affected / exposed                     | 83 / 4687 (1.77%) |  |  |
| occurrences causally related to treatment / all | 0 / 86            |  |  |
| deaths causally related to treatment / all      | 0 / 5             |  |  |
| Cerebrovascular disorder                        |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Cerebrovascular insufficiency                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cervical cord compression                       |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cervical myelopathy                             |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cervical radiculopathy                          |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cognitive disorder                              |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Complex partial seizures                        |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coordination abnormal                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dementia Alzheimer's type                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Diabetic neuropathy                             |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dizziness                                       |                   |  |  |
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dysarthria                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Embolic cerebral infarction                     |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Embololic stroke                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Encephalopathy                                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Epilepsy  |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Generalised tonic-clonic seizure                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Guillain-Barre syndrome                         |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhage intracranial                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhagic cerebral infarction                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhagic stroke                             |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Headache  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hemiparesis                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hemiplegia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydrocephalus                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypercapnic coma                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperkinesia                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypertensive encephalopathy                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoaesthesia                                   |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypoglycaemic coma                              |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypotonia                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| IIIrd nerve paralysis                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intercostal neuralgia                           |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ischaemic cerebral infarction                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ischaemic stroke                                |                   |  |  |
| subjects affected / exposed                     | 38 / 4687 (0.81%) |  |  |
| occurrences causally related to treatment / all | 2 / 42            |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Lacunar infarction                              |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Leukoencephalopathy                             |                   |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Loss of consciousness                           |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lumbar radiculopathy                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metabolic encephalopathy                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Migraine  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mononeuritis                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Monoplegia                                      |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscle spasticity                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myelitis transverse                             |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myelopathy                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myoclonus                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nerve root compression                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuroleptic malignant syndrome                  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuropathy peripheral                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paraesthesia                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paraplegia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paraparesis                                     |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Parkinson's disease                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Partial seizures                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral motor neuropathy                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peroneal nerve palsy                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Petit mal epilepsy                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Piriformis syndrome                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Presyncope                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radiculopathy                                   |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sciatica  |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Seizure   |                   |  |  |
| subjects affected / exposed                     | 12 / 4687 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 16            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sensory disturbance                             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Spinal cord compression                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Spinal epidural haematoma                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Subarachnoid haemorrhage                        |                   |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Spondylitic myelopathy                          |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Syncope   |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 27 / 4687 (0.58%) |  |  |
| occurrences causally related to treatment / all | 3 / 28            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Subdural hygroma                                |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thalamic infarction                             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombotic cerebral infarction                  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombotic stroke                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Transient ischaemic attack                      |                   |  |  |
| subjects affected / exposed                     | 53 / 4687 (1.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 54            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| VIIth nerve paralysis                           |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vascular encephalopathy                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vertebral artery dissection                     |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vertebral artery stenosis                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vertebrobasilar insufficiency                   |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vocal cord paresis                              |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders            |                   |  |  |
| Anaemia   |                   |  |  |
| subjects affected / exposed                     | 15 / 4687 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Coagulopathy                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Febrile neutropenia                             |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Haemorrhagic anaemia                            |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypereosinophilic syndrome                      |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypochromic anaemia                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypocoagulable state                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Iron deficiency anaemia                         |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Microcytic anaemia                              |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neutropenia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Normochromic normocytic anaemia                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ear and labyrinth disorders                     |                  |  |  |
| Deafness  |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cerumen impaction                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Deafness unilateral                             |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sudden hearing loss                             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Tinnitus  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Tympanic membrane perforation                   |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vertigo   |                   |  |  |
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 12            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vertigo positional                              |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Eye disorders                                   |                   |  |  |
| Amaurosis                                       |                   |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blindness                                       |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blindness unilateral                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cataract  |                   |  |  |
| subjects affected / exposed                     | 24 / 4687 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 29            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cataract cortical                               |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Corneal degeneration                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic retinopathy                            |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Exfoliation syndrome                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Glaucoma  |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Keratopathy                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Macular fibrosis                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Macular oedema                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Papilloedema                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal artery occlusion                        |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal detachment                              |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal haemorrhage                             |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinal tear                                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinoschisis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Retinopathy                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Visual acuity reduced                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vitreous haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vitreous opacities                              |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Abdominal hernia                                |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain                                  |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal hernia obstructive                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain lower                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain upper                            |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal fissure                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal fistula                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ascites   |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bezoar  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chronic gastritis                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis ischaemic                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colon dysplasia                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Crohn's disease                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dental caries                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetic gastroparesis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetic gastropathy                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diarrhoea                                       |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 12            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenal perforation                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diverticulum                                    |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diverticulum intestinal                         |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenal ulcer haemorrhage                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenal ulcer                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenal ulcer perforation                      |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Duodenitis                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dysphagia                                       |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dyspepsia                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enteritis                                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterocolitis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Erosive duodenitis                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Epigastric discomfort                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Food poisoning                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Faecaloma                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric haemorrhage                             |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric perforation                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric polyps                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric ulcer                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric ulcer haemorrhage                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastritis                                       |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastritis erosive                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric ulcer perforation                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastritis haemorrhagic                          |                  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastroduodenal ulcer                            |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal angiodysplasia                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastroduodenitis                                |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal disorder                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal haemorrhage                    |                   |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrooesophageal reflux disease                |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gingival bleeding                               |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal inflammation                   |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematochezia                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematemesis                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhoidal haemorrhage                       |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhoids                                    |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemorrhoids thrombosed                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hiatus hernia                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileus   |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileus paralytic                                 |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Impaired gastric emptying                       |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Incarcerated umbilical hernia                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inguinal hernia                                 |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inguinal hernia strangulated                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal haemorrhage                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal ischaemia                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Intestinal obstruction                          |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Irritable bowel syndrome                        |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal perforation                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestinal ulcer                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestine polyp                           |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestine perforation                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Localised intraabdominal fluid collection       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lumbar hernia                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mallory-Weiss syndrome                          |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Melaena   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nausea  |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mesenteric vein thrombosis                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophageal stenosis                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophagitis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis acute                              |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis chronic                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis relapsing                          |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peptic ulcer                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peptic ulcer haemorrhage                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peptic ulcer perforation                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peritoneal haemorrhage                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Rectal haemorrhage                              |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small intestinal obstruction                    |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stomatitis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Small intestinal perforation                    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subileus  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stress ulcer                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper gastrointestinal haemorrhage              |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Umbilical hernia                                |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombosis mesenteric vessel                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Varices oesophageal                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Volvulus  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vomiting  |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Angioedema                                      |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cold sweat                                      |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dermal cyst                                     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dermatitis contact                              |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic bullosis                               |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic foot                                   |                   |  |  |
| subjects affected / exposed                     | 21 / 4687 (0.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 24            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Eczema  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Erythema  |                   |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Erythrodermic psoriasis                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ingrowing nail                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Leukoplakia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuropathic ulcer                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pemphigus                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin fibrosis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin necrosis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin ulcer                                      |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 17 / 4687 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Skin ulcer haemorrhage                          |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urticaria                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal and urinary disorders                     |                   |  |  |
| Acute kidney injury                             |                   |  |  |
| subjects affected / exposed                     | 45 / 4687 (0.96%) |  |  |
| occurrences causally related to treatment / all | 4 / 46            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Acute prerenal failure                          |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Albuminuria                                     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bladder neck sclerosis                          |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Anuria  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bladder outlet obstruction                      |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Calculus bladder                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Calculus ureteric                               |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Calculus urinary                                |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis glandularis                            |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chronic kidney disease                          |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis haemorrhagic                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diabetic nephropathy                            |                  |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dysuria   |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Haematuria                                      |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hydronephrosis                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypertensive nephropathy                        |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Lower urinary tract symptoms                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Microalbuminuria                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Nephritis                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Nephrolithiasis                                 |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Nephropathy                                     |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nephrotic syndrome                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Obstructive uropathy                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oliguria  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Polyuria  |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal artery arteriosclerosis                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal artery stenosis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal colic                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cyst                                      |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal impairment                                |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal failure                                   |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Renal tubular necrosis                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal infarct                                   |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stress urinary incontinence                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tubulointerstitial nephritis                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ureteric obstruction                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urethral stenosis                               |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary bladder haemorrhage                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary bladder polyp                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary incontinence                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary retention                               |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract obstruction                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endocrine disorders                             |                  |  |  |
| Basedow's disease                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Goitre  |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperparathyroidism                             |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyperparathyroidism primary                     |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyperthyroidism                                 |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Arthritis                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bursitis  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bone fistula                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cervical spinal stenosis                        |                   |  |  |



|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Costochondritis                                 |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dupuytren's contracture                         |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Dactylitis                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Foot deformity                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Flank pain                                      |                  |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fistula   |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fracture nonunion                               |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fracture delayed union                          |                  |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gouty arthritis                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gouty tophus                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intervertebral disc compression                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intervertebral disc degeneration                |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intervertebral disc protrusion                  |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intervertebral disc disorder                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lumbar spinal stenosis                          |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lower extremity mass                            |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscle tightness                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscle twitching                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Muscular weakness                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal chest pain                      |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal pain                            |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal disorder                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myofascial pain syndrome                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myalgia   |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Myositis  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neck pain                                       |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neuropathic arthropathy                         |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteitis  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteitis deformans                              |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteoarthritis                                  |                   |  |  |
| subjects affected / exposed                     | 32 / 4687 (0.68%) |  |  |
| occurrences causally related to treatment / all | 0 / 34            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomalacia                                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteonecrosis                                   |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Osteoporosis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Osteoporotic fracture                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pain in extremity                               |                  |  |  |
| subjects affected / exposed                     | 9 / 4687 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pathological fracture                           |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Periarthritis                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rhabdomyolysis                                  |                  |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rotator cuff syndrome                           |                  |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal column stenosis                          |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal osteoarthritis                           |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal pain                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spondylitis                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spondylolisthesis                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Synovitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tendonitis                                      |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tenosynovitis stenosans                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Trigger finger                                  |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infections and infestations                     |                  |  |  |
| Abdominal abscess                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal wall abscess                          |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abscess   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abscess limb                                    |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abscess of eyelid                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Acute sinusitis                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Amoebiasis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Amoebic dysentery                               |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal abscess                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Appendicitis                                    |                  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Appendicitis perforated                         |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Arteriosclerotic gangrene                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Arthritis bacterial                             |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Atypical pneumonia                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bacteraemia                                     |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bacterial sepsis                                |                  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Biliary tract infection                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bone abscess                                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchiolitis                                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchitis                                      |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchitis viral                                |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bronchopneumonia                                |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Catheter site infection                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cellulitis                                      |                   |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 28 / 4687 (0.60%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 37            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cellulitis gangrenous                           |                   |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cellulitis of male external genital organ       |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cellulitis staphylococcal                       |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cholecystitis infective                         |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Chronic sinusitis                               |                   |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Clostridium difficile colitis                   |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cutaneous larva migrans                         |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cystitis  |                   |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cystitis bacterial                              |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dengue fever                                    |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Device related infection                        |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic foot infection                         |                   |  |  |
| subjects affected / exposed                     | 12 / 4687 (0.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 14            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Device related sepsis                           |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diverticulitis                                  |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic gangrene                               |                   |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Eczema infected                                 |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ear infection                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endocarditis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Empyema   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterocolitis infectious                        |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterocolitis viral                             |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endophthalmitis                                 |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Epididymitis                                    |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Erysipelas                                      |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Escherichia urinary tract infection             |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Escherichia sepsis                              |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Furuncle  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Febrile infection                               |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastroenteritis                                 |                   |  |  |
| subjects affected / exposed                     | 33 / 4687 (0.70%) |  |  |
| occurrences causally related to treatment / all | 3 / 35            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gallbladder empyema                             |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gangrene  |                   |  |  |
| subjects affected / exposed                     | 16 / 4687 (0.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastroenteritis salmonella                      |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastroenteritis viral                           |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal infection                      |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal protozoal infection            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Giardiasis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| H1N1 influenza                                  |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infected skin ulcer                             |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infectious colitis                              |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Incision site infection                         |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infectious pleural effusion                     |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Influenza                                       |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inguinal hernia gangrenous                      |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infusion site infection                         |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal fistula infection                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal tuberculosis                         |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Kidney infection                                |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Klebsiella infection                            |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Labyrinthitis                                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Liver abscess                                   |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lobar pneumonia                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Localised infection                             |                   |  |  |
| subjects affected / exposed                     | 6 / 4687 (0.13%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lower respiratory tract infection               |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lower respiratory tract infection bacterial     |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lung infection                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lyme disease                                    |                   |  |  |



|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Mediastinitis                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Meningitis                                      |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Meningitis bacterial                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Meningitis streptococcal                        |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Meningitis tuberculous                          |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Muscle abscess                                  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Myelitis  |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Nasal abscess                                   |                  |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Oesophageal candidiasis                         |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomyelitis acute                             |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomyelitis                                   |                   |  |  |
| subjects affected / exposed                     | 14 / 4687 (0.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomyelitis bacterial                         |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Osteomyelitis chronic                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Otitis externa                                  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Otitis media                                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Peritonitis                                     |                   |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 5 / 4687 (0.11%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Periodontitis                                   |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Peritonsillar abscess                           |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pertussis                                       |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pharyngotonsillitis                             |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pneumonia                                       |                   |  |  |  |
| subjects affected / exposed                     | 79 / 4687 (1.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 86            |  |  |  |
| deaths causally related to treatment / all      | 0 / 6             |  |  |  |
| Pneumonia bacterial                             |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pneumonia fungal                                |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pneumonia influenzal                            |                   |  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia haemophilus                           |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia pneumococcal                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural infection                       |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Postoperative wound infection                   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural sepsis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pseudomonal sepsis                              |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Prostatic abscess                               |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary mycosis                               |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psoas abscess                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary tuberculosis                          |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis acute                            |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 2 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis                                  |                  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Respiratory tract infection                     |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis chronic                          |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Salmonellosis                                   |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rotavirus infection                             |                  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rhinitis  |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sepsis  |                   |  |  |
| subjects affected / exposed                     | 13 / 4687 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 13            |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Scrotal abscess                                 |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Septic encephalopathy                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Septic shock                                    |                   |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 1 / 7             |  |  |
| deaths causally related to treatment / all      | 1 / 3             |  |  |
| Sinusitis                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin infection                                  |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Staphylococcal skin infection                   |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Staphylococcal sepsis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Staphylococcal infection                        |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subcutaneous abscess                            |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tonsillitis                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tuberculosis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tracheobronchitis                               |                  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tuberculous pleurisy                            |                  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper respiratory tract infection               |                  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Urinary tract infection pseudomonal             |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Urinary tract infection                         |                   |  |  |  |
| subjects affected / exposed                     | 29 / 4687 (0.62%) |  |  |  |
| occurrences causally related to treatment / all | 9 / 30            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Urinary tract infection fungal                  |                   |  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Urosepsis                                       |                   |  |  |  |
| subjects affected / exposed                     | 17 / 4687 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 6 / 18            |  |  |  |
| deaths causally related to treatment / all      | 2 / 2             |  |  |  |
| Vaginal cellulitis                              |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Vestibular neuronitis                           |                   |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Varicella                                       |                   |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Viral infection                                 |                   |  |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Wound infection                                 |                   |  |  |
| subjects affected / exposed                     | 7 / 4687 (0.15%)  |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Wound sepsis                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Metabolism and nutrition disorders              |                   |  |  |
| Decreased appetite                              |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Dehydration                                     |                   |  |  |
| subjects affected / exposed                     | 10 / 4687 (0.21%) |  |  |
| occurrences causally related to treatment / all | 2 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetes mellitus                               |                   |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%)  |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Diabetes mellitus inadequate control            |                   |  |  |
| subjects affected / exposed                     | 11 / 4687 (0.23%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic complication                           |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diabetic ketoacidosis                           |                   |  |  |

|   |                  |  |  |  |
|---|------------------|--|--|--|
| subjects affected / exposed                     | 4 / 4687 (0.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Diabetic metabolic decompensation               |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fluid overload                                  |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Gout  |                  |  |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hyperglycaemia                                  |                  |  |  |  |
| subjects affected / exposed                     | 8 / 4687 (0.17%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 8            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hyperkalaemia                                   |                  |  |  |  |
| subjects affected / exposed                     | 5 / 4687 (0.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hypernatraemia                                  |                  |  |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hypervolaemia                                   |                  |  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Hypoglycaemia                                   |                  |  |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 19 / 4687 (0.41%) |  |  |
| occurrences causally related to treatment / all | 6 / 20            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypomagnesaemia                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypokalaemia                                    |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hyponatraemia                                   |                   |  |  |
| subjects affected / exposed                     | 4 / 4687 (0.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypovolaemia                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Insulin resistance                              |                   |  |  |
| subjects affected / exposed                     | 0 / 4687 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lactic acidosis                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Metabolic acidosis                              |                   |  |  |
| subjects affected / exposed                     | 2 / 4687 (0.04%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Lipomatosis                                     |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Obesity   |                  |  |  |
| subjects affected / exposed                     | 3 / 4687 (0.06%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Type 2 diabetes mellitus                        |                  |  |  |
| subjects affected / exposed                     | 1 / 4687 (0.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

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

| <b>Non-serious adverse events</b>                     | Placebo              | Empagliflozin 10 mg  | Empagliflozin 25 mg  |
|---|----------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events |                      |                      |                      |
| subjects affected / exposed                           | 1690 / 2333 (72.44%) | 1556 / 2345 (66.35%) | 1551 / 2342 (66.23%) |
| Vascular disorders                                    |                      |                      |                      |
| Hypertension  |                      |                      |                      |
| subjects affected / exposed                           | 210 / 2333 (9.00%)   | 154 / 2345 (6.57%)   | 176 / 2342 (7.51%)   |
| occurrences (all)                                     | 251                  | 176                  | 209                  |
| Nervous system disorders                              |                      |                      |                      |
| Dizziness   |                      |                      |                      |
| subjects affected / exposed                           | 151 / 2333 (6.47%)   | 170 / 2345 (7.25%)   | 173 / 2342 (7.39%)   |
| occurrences (all)                                     | 198                  | 215                  | 245                  |
| Headache  |                      |                      |                      |
| subjects affected / exposed                           | 123 / 2333 (5.27%)   | 100 / 2345 (4.26%)   | 124 / 2342 (5.29%)   |
| occurrences (all)                                     | 158                  | 146                  | 166                  |
| General disorders and administration site conditions  |                      |                      |                      |
| Oedema peripheral                                     |                      |                      |                      |
| subjects affected / exposed                           | 155 / 2333 (6.64%)   | 84 / 2345 (3.58%)    | 75 / 2342 (3.20%)    |
| occurrences (all)                                     | 171                  | 96                   | 83                   |
| Gastrointestinal disorders                            |                      |                      |                      |
| Constipation  |                      |                      |                      |

|   |                            |                            |                            |
|---|----------------------------|----------------------------|----------------------------|
| subjects affected / exposed<br>occurrences (all)  | 109 / 2333 (4.67%)<br>117  | 91 / 2345 (3.88%)<br>99    | 119 / 2342 (5.08%)<br>130  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 171 / 2333 (7.33%)<br>217  | 145 / 2345 (6.18%)<br>184  | 144 / 2342 (6.15%)<br>169  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)      | 146 / 2333 (6.26%)<br>177  | 119 / 2345 (5.07%)<br>133  | 108 / 2342 (4.61%)<br>124  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 130 / 2333 (5.57%)<br>142  | 107 / 2345 (4.56%)<br>119  | 148 / 2342 (6.32%)<br>169  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 148 / 2333 (6.34%)<br>181  | 149 / 2345 (6.35%)<br>168  | 166 / 2342 (7.09%)<br>178  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 133 / 2333 (5.70%)<br>147  | 114 / 2345 (4.86%)<br>128  | 101 / 2342 (4.31%)<br>113  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 164 / 2333 (7.03%)<br>223  | 129 / 2345 (5.50%)<br>157  | 117 / 2342 (5.00%)<br>150  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)   | 165 / 2333 (7.07%)<br>237  | 134 / 2345 (5.71%)<br>181  | 149 / 2342 (6.36%)<br>191  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 217 / 2333 (9.30%)<br>301  | 210 / 2345 (8.96%)<br>291  | 220 / 2342 (9.39%)<br>289  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                             | 199 / 2333 (8.53%)<br>266  | 191 / 2345 (8.14%)<br>266  | 175 / 2342 (7.47%)<br>266  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                       | 344 / 2333 (14.74%)<br>538 | 339 / 2345 (14.46%)<br>598 | 337 / 2342 (14.39%)<br>578 |

|                                    |                        |                        |                        |
|------------------------------------|------------------------|------------------------|------------------------|
| Metabolism and nutrition disorders |                        |                        |                        |
| Hyperglycaemia                     |                        |                        |                        |
| subjects affected / exposed        | 423 / 2333<br>(18.13%) | 217 / 2345 (9.25%)     | 202 / 2342 (8.63%)     |
| occurrences (all)                  | 1188                   | 442                    | 405                    |
| Hypoglycaemia                      |                        |                        |                        |
| subjects affected / exposed        | 685 / 2333<br>(29.36%) | 694 / 2345<br>(29.59%) | 673 / 2342<br>(28.74%) |
| occurrences (all)                  | 5225                   | 4199                   | 4246                   |

|   |                         |  |  |
|---|-------------------------|--|--|
| <b>Non-serious adverse events</b>                     | All Empagliflozin       |  |  |
| Total subjects affected by non-serious adverse events |                         |  |  |
| subjects affected / exposed                           | 3107 / 4687<br>(66.29%) |  |  |
| Vascular disorders                                    |                         |  |  |
| Hypertension  |                         |  |  |
| subjects affected / exposed                           | 330 / 4687 (7.04%)      |  |  |
| occurrences (all)                                     | 385                     |  |  |
| Nervous system disorders                              |                         |  |  |
| Dizziness   |                         |  |  |
| subjects affected / exposed                           | 343 / 4687 (7.32%)      |  |  |
| occurrences (all)                                     | 460                     |  |  |
| Headache  |                         |  |  |
| subjects affected / exposed                           | 224 / 4687 (4.78%)      |  |  |
| occurrences (all)                                     | 312                     |  |  |
| General disorders and administration site conditions  |                         |  |  |
| Oedema peripheral                                     |                         |  |  |
| subjects affected / exposed                           | 159 / 4687 (3.39%)      |  |  |
| occurrences (all)                                     | 179                     |  |  |
| Gastrointestinal disorders                            |                         |  |  |
| Constipation  |                         |  |  |
| subjects affected / exposed                           | 210 / 4687 (4.48%)      |  |  |
| occurrences (all)                                     | 229                     |  |  |
| Diarrhoea   |                         |  |  |
| subjects affected / exposed                           | 289 / 4687 (6.17%)      |  |  |
| occurrences (all)                                     | 353                     |  |  |
| Respiratory, thoracic and mediastinal disorders       |                         |  |  |
| Cough   |                         |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed                     | 227 / 4687 (4.84%)   |  |  |
| occurrences (all)                               | 257                  |  |  |
| Musculoskeletal and connective tissue disorders |                      |  |  |
| Arthralgia                                      |                      |  |  |
| subjects affected / exposed                     | 255 / 4687 (5.44%)   |  |  |
| occurrences (all)                               | 288                  |  |  |
| Back pain                                       |                      |  |  |
| subjects affected / exposed                     | 315 / 4687 (6.72%)   |  |  |
| occurrences (all)                               | 346                  |  |  |
| Pain in extremity                               |                      |  |  |
| subjects affected / exposed                     | 215 / 4687 (4.59%)   |  |  |
| occurrences (all)                               | 241                  |  |  |
| Infections and infestations                     |                      |  |  |
| Bronchitis                                      |                      |  |  |
| subjects affected / exposed                     | 246 / 4687 (5.25%)   |  |  |
| occurrences (all)                               | 307                  |  |  |
| Influenza                                       |                      |  |  |
| subjects affected / exposed                     | 283 / 4687 (6.04%)   |  |  |
| occurrences (all)                               | 372                  |  |  |
| Nasopharyngitis                                 |                      |  |  |
| subjects affected / exposed                     | 430 / 4687 (9.17%)   |  |  |
| occurrences (all)                               | 580                  |  |  |
| Upper respiratory tract infection               |                      |  |  |
| subjects affected / exposed                     | 366 / 4687 (7.81%)   |  |  |
| occurrences (all)                               | 532                  |  |  |
| Urinary tract infection                         |                      |  |  |
| subjects affected / exposed                     | 676 / 4687 (14.42%)  |  |  |
| occurrences (all)                               | 1176                 |  |  |
| Metabolism and nutrition disorders              |                      |  |  |
| Hyperglycaemia                                  |                      |  |  |
| subjects affected / exposed                     | 419 / 4687 (8.94%)   |  |  |
| occurrences (all)                               | 847                  |  |  |
| Hypoglycaemia                                   |                      |  |  |
| subjects affected / exposed                     | 1367 / 4687 (29.17%) |  |  |
| occurrences (all)                               | 8445                 |  |  |





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 22 September 2010 | <p>With the introduction of this amendment, cardiovascular outcome events were exempt from the expedited unblinded reporting process if they occurred during the randomised treatment period to preclude reporting of unblinded outcome events while this double-blind study was ongoing. Cardiovascular outcome events were to be reported in specific eCRF pages instead of on paper SAE forms since the reporting of outcome events by treatment group during the trial (by anyone except the DMC) could potentially jeopardise the integrity of the trial. Cardiovascular outcome events that occurred during the screening/run in phase were to be considered as SAEs and not as outcome events. Additionally, hepatic injury was added a significant AE to comply with FDA guidelines for DILI.</p>  |
| 22 April 2011     | <p>Inclusion criterion:Maximum HbA1c for treatment naïve patients was raised to 9.0% from 8.0% and definition of patients with high CV risk was expanded to include single vessel disease,and further clarification of criteria to be met for inclusion of patients with peripheral artery disease,unstable angina,multivessel disease was provided.</p> <p>Exclusion criteria:Acute coronary syndrome, stroke or TIA within 2 months prior to informed consent was added; sibutramine and orlistat were removed as specifically named anti-obesity drugs.</p> <p>Duration of follow-up after regular completion of treatment period was increased from 1 to 4 weeks.</p> <p>Endpoints:Primary endpoint wording was clarified to indicate when patients without events would be censored,Weight and waist circumference measurements at Week 12 were added as further endpoints, Heart failure requiring hospitalization moved from tertiary CV endpoints to secondary endpoints; composite microvascular outcome added as secondary endpoint; Hospitalisation for unstable angina and components of microvascular composite endpoint added as tertiary endpoints.With regard to hypoglycaemic events to be documented in the eCRF,every episode of plasma glucose below 70 was corrected to <math>\leq 70</math> mg/dL (3.9 mmol/L).</p> <p>Clarification of safety laboratory assessments procedures.</p> <p>Statistical analyses:Age &amp; gender were added as covariates to primary analysis model; clarification of non-inferiority margin and order of testing for primary, secondary endpoints both for non-inferiority and then superiority;a 4-step hierarchical testing strategy to include key secondary endpoint was specified.</p> <p>Trial design description was clarified to indicate that randomisation would be stopped after 4000 patients had been randomised.</p> <p>Clarified that while there was no interim analysis planned on the trial level, there was a pre-specified meta-analysis to assess the cardiovascular safety profile of empagliflozin, which included data from this trial.</p> |

|                  |   |
|------------------|---|
| 29 December 2011 | <p>The non-inferiority margin of 1.8 and the 2 corresponding tests (of the primary and key secondary endpoint), defined as steps 1 and 2 in the hierarchical testing strategy were removed. Hence the test for non-inferiority of the primary endpoint using the non-inferiority margin of 1.3 was defined to be the first test, followed by testing non inferiority of key secondary endpoint etc. Number of patients with primary endpoint events required was changed from 137 to 691 to ensure a power of 90% for testing non-inferiority based on margin of 1.3, using an overall one-sided alpha of 0.025 and 0.0249 for the final analysis.</p> <p>Total number of planned randomised patients was increased from 4000 to 7000 . Planned treatment duration of the patients was changed from an anticipated 206 weeks to approximately 300 to 420 weeks.</p> <p>An interim analysis of this trial to support a New Drug Application (NDA) was part of the cardiovascular meta-analysis using the interim data of this trial. It was projected that approximately 80 confirmed primary events would have been observed from this trial at that time. The interim analysis and the cardiovascular meta-analysis were to be performed by a team independent from the 1245.25 trial team so that the trial team remained blinded to the results.</p> <p>A Haybittle-Peto boundary was used to maintain the experiment-wise overall <math>\alpha</math> level of 0.025.</p> <p>Clarification, that primary &amp; key secondary endpoints did not include silent MI. Further secondary endpoints were revised to new onset albuminuria defined as UACR <math>\geq 30</math> mg/g and new onset macroalbuminuria <math>\geq 300</math> mg/g.</p> <p>Death due to renal disease was added to definition of new or worsening nephropathy.</p> <p>Weight &amp; waist circumference were to be measured annually.</p> <p>hs CR, hs Troponin T, cystatin C, indicators of cardiac risk were to be measured.</p> <p>Procedures for clinical evaluation of liver injury were added.</p> <p>An additional sample for assessment of PK in AESIs was to be collected.</p> |
| 15 October 2013  | <p>Main changes:</p> <ul style="list-style-type: none"> <li>- Clarification that the follow-up period of 4 weeks means 30 days</li> <li>- Procedures to be performed for patients on study medication at the time of study completion were clarified</li> <li>- It was clarified that a minimum of 691 events for the planned primary analysis referred to 3-point MACE</li> <li>- The central adjudication of malignancies and hepatic events was added</li> </ul>   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

2 sets of duplicates (4 patients (pts) ) were counted only once. 652 sites were initiated and 611 enrolled. One site transferred all pts to other sites. 27 pts randomised and 13 pts screened were excluded from analyses due to serious non-compliance

Notes: