



## Clinical trial results:

### An Open Label, Single Arm, Extension Study to Evaluate the Long Term Safety and Sustained Efficacy of Denosumab (AMG162) in the Treatment of Postmenopausal Osteoporosis

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2007-001041-17   |
| Trial protocol           | DK SE EE DE LV GB LT HU AT FI BE MT CZ FR ES GR IT BG SK |
| Global end of trial date | 29 July 2015   |

#### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 01 April 2017  |
| First version publication date | 04 August 2016   |
| Version creation reason        | • New data added to full data set<br>add histomorphology endpoint data |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20060289 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00523341 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Amgen, inc.  |
| Sponsor organisation address | One Amgen Center Drive, Thousand oaks, CA, United States, 91320                          |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH,<br>MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH,<br>MedInfoInternational@amgen.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                       | 29 July 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 29 July 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to describe the safety and tolerability of up to 10 years or 7 years denosumab administration as measured by adverse event monitoring, immunogenicity and safety laboratory parameters in participants who previously received denosumab or placebo, respectively.

Protection of trial subjects:

This study was conducted in accordance with the principles of the Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 07 August 2007 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Poland: 496         |
| Country: Number of subjects enrolled | Denmark: 898        |
| Country: Number of subjects enrolled | Czech Republic: 381 |
| Country: Number of subjects enrolled | United Kingdom: 327 |
| Country: Number of subjects enrolled | Estonia: 296        |
| Country: Number of subjects enrolled | Brazil: 287         |
| Country: Number of subjects enrolled | Argentina: 211      |
| Country: Number of subjects enrolled | United States: 178  |
| Country: Number of subjects enrolled | Spain: 165          |
| Country: Number of subjects enrolled | Hungary: 132        |
| Country: Number of subjects enrolled | Italy: 132          |
| Country: Number of subjects enrolled | Germany: 116        |
| Country: Number of subjects enrolled | Norway: 98          |
| Country: Number of subjects enrolled | Austria: 86         |
| Country: Number of subjects enrolled | Belgium: 84         |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | France: 83      |
| Country: Number of subjects enrolled | Sweden: 78      |
| Country: Number of subjects enrolled | Latvia: 75      |
| Country: Number of subjects enrolled | Mexico: 72      |
| Country: Number of subjects enrolled | Canada: 66      |
| Country: Number of subjects enrolled | Slovakia: 52    |
| Country: Number of subjects enrolled | Lithuania: 45   |
| Country: Number of subjects enrolled | Switzerland: 40 |
| Country: Number of subjects enrolled | New Zealand: 33 |
| Country: Number of subjects enrolled | Australia: 25   |
| Country: Number of subjects enrolled | Bulgaria: 25    |
| Country: Number of subjects enrolled | Finland: 19     |
| Country: Number of subjects enrolled | Greece: 15      |
| Country: Number of subjects enrolled | Malta: 15       |
| Country: Number of subjects enrolled | Serbia: 15      |
| Country: Number of subjects enrolled | Romania: 5      |
| Worldwide total number of subjects   | 4550            |
| EEA total number of subjects         | 3623            |

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)                      | 107  |
| From 65 to 84 years                       | 4304 |
| 85 years and over                         | 139  |

## Subject disposition

### Recruitment

Recruitment details:

This was an extension study open to participants who had completed core study 20030216 (NCT00089791). The study was conducted at 178 centers in North America, South America, Europe, Australia, and New Zealand. Participants were enrolled from 7 August 2007 to 20 June 2008.

### Pre-assignment

Screening details:

All participants received open-label denosumab during this study. Results are reported by the Study 20030216 randomized treatment groups (placebo versus denosumab).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Denosumab                                    |
| Investigational medicinal product code | AMG 162                                      |
| Other name                             | Prolia                                       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Administered by subcutaneous injection once every 6 months.

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

Arm description:

Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Denosumab                                    |
| Investigational medicinal product code | AMG 162                                      |
| Other name                             | Prolia                                       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Administered by subcutaneous injection once every 6 months.

| <b>Number of subjects in period 1</b> | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |
|---------------------------------------|------------------------|--------------------------|
| Started                               | 2207                   | 2343                     |
| Received Treatment                    | 2206                   | 2343                     |
| Completed                             | 1283                   | 1343                     |
| Not completed                         | 924                    | 1000                     |
| Consent withdrawn by subject          | 399                    | 427                      |
| Physician decision                    | 14                     | 13                       |
| Ineligibility Determined              | 3                      | 4                        |
| Adverse event, non-fatal              | 122                    | 155                      |
| Protocol Deviation                    | 6                      | 5                        |
| Other                                 | 181                    | 198                      |
| Death                                 | 101                    | 110                      |
| Non-compliance                        | 20                     | 13                       |
| Lost to follow-up                     | 73                     | 61                       |
| Requirement for Alternative Therapy   | 4                      | 14                       |
| Disease Progression                   | 1                      | -                        |

## Baseline characteristics

### Reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Placebo / Denosumab   |
| Reporting group description:  |                       |
| Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.                                 |                       |
| Reporting group title   | Denosumab / Denosumab |
| Reporting group description:  |                       |
| Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment). |                       |

| Reporting group values  | Placebo / Denosumab | Denosumab / Denosumab | Total |
|---|---------------------|-----------------------|-------|
| Number of subjects  | 2207                | 2343                  | 4550  |
| Age, Customized<br>Units: participants  |                     |                       |       |
| 60 - 64 years   | 58                  | 49                    | 107   |
| 65 - 69 years   | 326                 | 320                   | 646   |
| 70 - 74 years   | 672                 | 716                   | 1388  |
| ≥ 75 years  | 1151                | 1258                  | 2409  |
| Age Continuous<br>Units: years  |                     |                       |       |
| arithmetic mean   | 74.8                | 74.9                  |       |
| standard deviation  | ± 5.1               | ± 5                   | -     |
| Gender, Male/Female<br>Units: participants  |                     |                       |       |
| Female  | 2207                | 2343                  | 4550  |
| Male  | 0                   | 0                     | 0     |
| Race/Ethnicity, Customized<br>Units: Subjects   |                     |                       |       |
| White   | 2063                | 2169                  | 4232  |
| Black   | 16                  | 19                    | 35    |
| Hispanic or Latino  | 121                 | 145                   | 266   |
| Asian   | 2                   | 3                     | 5     |
| Japanese  | 3                   | 5                     | 8     |
| Native Hawaiian or Other Pacific Islander   | 1                   | 0                     | 1     |
| Other   | 1                   | 2                     | 3     |
| Bone Mineral Density T-score   Lumbar spine   |                     |                       |       |
| <p>The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old.</p> <p>Normal is a T-score of -1.0 or higher;</p> <p>Osteopenia is defined as between -1.0 and -2.5;</p> <p>Osteoporosis is defined as -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> |                     |                       |       |
| Units: T-score  |                     |                       |       |
| arithmetic mean   | -2.81               | -2.14                 |       |
| standard deviation  | ± 0.75              | ± 0.8                 | -     |
| Bone Mineral Density T-score   Total hip  |                     |                       |       |

|   |                     |                     |   |
|---|---------------------|---------------------|---|
| <p>The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old.<br/> Normal is a T-score of <math>-1.0</math> or higher;<br/> Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>;<br/> Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> |                     |                     |   |
| Units: T-score<br>arithmetic mean<br>standard deviation   | -1.93<br>$\pm 0.8$  | -1.5<br>$\pm 0.79$  | - |
| Bone Mineral Density T-score   Femoral neck   |                     |                     |   |
| <p>The T-score is the bone mineral density (BMD) at the site when compared to that of a healthy thirty-year-old.<br/> Normal is a T-score of <math>-1.0</math> or higher;<br/> Osteopenia is defined as between <math>-1.0</math> and <math>-2.5</math>;<br/> Osteoporosis is defined as <math>-2.5</math> or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.</p> |                     |                     |   |
| Units: T-score<br>arithmetic mean<br>standard deviation   | -2.17<br>$\pm 0.72$ | -1.83<br>$\pm 0.75$ | - |
| Bone Mineral Density T-score at Study 20030216 Baseline   Lumbar spine  |                     |                     |   |
| Units: T-score<br>arithmetic mean<br>standard deviation   | -2.84<br>$\pm 0.68$ | -2.83<br>$\pm 0.67$ | - |
| Bone Mineral Density T-score at Study 20030216 Baseline   Total hip   |                     |                     |   |
| Units: T-score<br>arithmetic mean<br>standard deviation   | -1.85<br>$\pm 0.79$ | -1.85<br>$\pm 0.79$ | - |
| Bone Mineral Density T-score at Study 20030216 Baseline   Femoral neck  |                     |                     |   |
| Units: T-score<br>arithmetic mean<br>standard deviation   | -2.11<br>$\pm 0.71$ | -2.11<br>$\pm 0.71$ | - |

## End points

### End points reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Placebo / Denosumab   |
| Reporting group description:  |                       |
| Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.                                 |                       |
| Reporting group title   | Denosumab / Denosumab |
| Reporting group description:  |                       |
| Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment). |                       |

### Primary: Number of participants with Adverse Events (AEs)

|   |   |
|---|---|
| End point title   | Number of participants with Adverse Events (AEs) <sup>[1]</sup> |
| End point description:  |   |
| A serious adverse event (SAE) is defined as an AE that:   |   |
| <ul style="list-style-type: none"><li>• is fatal</li><li>• is life threatening</li><li>• requires in-patient hospitalization or prolongation of existing hospitalization</li><li>• results in persistent or significant disability/incapacity</li><li>• is a congenital anomaly/birth defect</li><li>• is other significant medical hazard.</li></ul>   |   |
| Treatment-related adverse events includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by study drug. The following were classified as adverse events of interest (events that are considered to be identified or potential risks of denosumab treatment): positively adjudicated osteonecrosis of the jaw, positively adjudicated atypical femoral fracture, hypocalcemia, adverse events potentially related to hypersensitivity, serious infection (including bacterial cellulitis), malignancy, cardiac disorders, vascular disorders, fracture healing complications, eczema, acute pancreatitis, and musculoskeletal pain. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| 84 months   |   |

Notes:

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

Justification: No formal statistical testing was performed.

| End point values                           | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                         | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                | 2206                | 2343                  |  |  |
| Units: participants                        |                     |                       |  |  |
| number (not applicable)                    |                     |                       |  |  |
| Any adverse event (AE)                     | 2070                | 2173                  |  |  |
| Serious adverse event                      | 945                 | 1014                  |  |  |
| Fatal adverse event                        | 101                 | 108                   |  |  |
| AE leading to study discontinuation        | 145                 | 173                   |  |  |
| AE leading to discontinuation of denosumab | 184                 | 216                   |  |  |
| Treatment-related adverse events (TRAE)    | 185                 | 188                   |  |  |
| Serious treatment-related adverse events   | 26                  | 28                    |  |  |

|  |      |      |  |  |
|--|------|------|--|--|
| Fatal treatment-related adverse events           | 1    | 0    |  |  |
| TRAE leading to study discontinuation            | 16   | 9    |  |  |
| TRAE leading to discontinuation of denosumab     | 30   | 25   |  |  |
| Positively adjudicated osteonecrosis of the jaw  | 6    | 7    |  |  |
| Positively adjudicated atypical femoral fracture | 1    | 1    |  |  |
| Hypocalcaemia                                    | 10   | 6    |  |  |
| AEs potentially related to hypersensitivity      | 260  | 280  |  |  |
| Serious infections                               | 161  | 185  |  |  |
| Serious bacterial cellulitis                     | 7    | 12   |  |  |
| Malignancy                                       | 227  | 237  |  |  |
| Cardiac disorders                                | 449  | 492  |  |  |
| Vascular disorders                               | 693  | 732  |  |  |
| Fracture healing complications                   | 0    | 1    |  |  |
| Eczema   | 99   | 115  |  |  |
| Acute pancreatitis                               | 4    | 8    |  |  |
| Musculoskeletal pain                             | 1125 | 1206 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Laboratory Toxicities of Grade $\geq 3$

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Laboratory Toxicities of Grade $\geq 3$ |
|-----------------|---|

End point description:

Laboratory toxicity grading was based on Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grade 3 indicates severe toxicity and Grade 4 indicates life-threatening toxicity.

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

End point timeframe:

84 months

Notes:

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

Justification: No formal statistical testing was performed.

| End point values            | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|-----------------------------|---------------------|-----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed | 2206                | 2343                  |  |  |
| Units: participants         |                     |                       |  |  |
| number (not applicable)     |                     |                       |  |  |
| Low sodium - Grade 3        | 28                  | 25                    |  |  |
| Low sodium - Grade 4        | 1                   | 0                     |  |  |
| High potassium - Grade 3    | 9                   | 11                    |  |  |
| High potassium - Grade 4    | 0                   | 3                     |  |  |
| Low potassium - Grade 3     | 7                   | 7                     |  |  |
| Low magnesium - Grade 3     | 1                   | 1                     |  |  |
| Low magnesium - Grade 4     | 0                   | 1                     |  |  |

|  |    |    |  |  |
|--|----|----|--|--|
| High calcium - Grade 3                           | 2  | 3  |  |  |
| High calcium - Grade 4                           | 0  | 2  |  |  |
| High corrected calcium - Grade 3                 | 2  | 3  |  |  |
| High corrected calcium - Grade 4                 | 0  | 2  |  |  |
| Low phosphorus - Grade 3                         | 3  | 1  |  |  |
| High Creatinine - Grade 3                        | 0  | 1  |  |  |
| High aspartate amino transferase (AST) - Grade 3 | 5  | 11 |  |  |
| High aspartate amino transferase (AST) - Grade 4 | 1  | 0  |  |  |
| High alanine amino transferase (ALT) - Grade 3   | 8  | 10 |  |  |
| High alanine amino transferase (ALT) - Grade 4   | 1  | 0  |  |  |
| High total bilirubin - Grade 3                   | 2  | 3  |  |  |
| Low albumin - Grade 3                            | 0  | 1  |  |  |
| High glucose - Grade 3                           | 35 | 37 |  |  |
| High glucose - Grade 4                           | 0  | 1  |  |  |
| Low glucose - Grade 3                            | 4  | 1  |  |  |
| Low glucose - Grade 4                            | 1  | 1  |  |  |
| Low hemoglobin - Grade 3                         | 6  | 4  |  |  |
| Low platelets - Grade 3                          | 3  | 7  |  |  |
| Low platelets - Grade 4                          | 2  | 4  |  |  |
| Low white blood cells - Grade 3                  | 5  | 7  |  |  |
| Low white blood cells - Grade 4                  | 0  | 1  |  |  |
| Low lymphocytes - Grade 3                        | 17 | 16 |  |  |
| Low lymphocytes - Grade 4                        | 2  | 1  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Antibodies to Denosumab

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Antibodies to Denosumab <sup>[3]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Every 12 months through Month 84

Notes:

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

Justification: No formal statistical testing was performed.

| End point values            | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|-----------------------------|---------------------|-----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed | 2206                | 2343                  |  |  |
| Units: participants         |                     |                       |  |  |
| number (not applicable)     | 1                   | 0                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Lumbar Spine Bone Mineral Density by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Lumbar Spine Bone Mineral Density by Visit |
|-----------------|--|

End point description:

Lumbar spine bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

End point timeframe:

Baseline (of extension study) and months 12, 24, 36, 60 and 84

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 2089                | 2210                  |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 2040, 2168)                    | 5.2 (5 to 5.3)      | 2 (1.8 to 2.2)        |  |  |
| Month 24 (n = 1935, 2061)                    | 7.7 (7.5 to 7.9)    | 3.5 (3.4 to 3.7)      |  |  |
| Month 36 (n = 1497, 1607)                    | 9.4 (9.1 to 9.6)    | 4.9 (4.7 to 5.1)      |  |  |
| Month 60 (n = 1472, 1567)                    | 13 (12.7 to 13.3)   | 7.9 (7.6 to 8.2)      |  |  |
| Month 84 (n = 1223, 1264)                    | 16.5 (16.1 to 16.9) | 10.8 (10.4 to 11.2)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Total Hip Bone Mineral Density by Visit

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Total Hip Bone Mineral Density by Visit |
|-----------------|---|

End point description:

Total hip bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline (of extension study) and months 12, 24, 36, 60 and 84 |           |

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 2089                | 2210                  |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 2029, 2160)                    | 3 (2.8 to 3.1)      | 0.8 (0.7 to 0.9)      |  |  |
| Month 24 (n = 1918, 2045)                    | 4.1 (4 to 4.2)      | 1.4 (1.3 to 1.5)      |  |  |
| Month 36 (n = 1475, 1591)                    | 4.9 (4.7 to 5)      | 1.8 (1.7 to 2)        |  |  |
| Month 60 (n = 1439, 1538)                    | 6.2 (6 to 6.4)      | 2.6 (2.4 to 2.8)      |  |  |
| Month 84 (n = 1200, 1232)                    | 7.4 (7.1 to 7.6)    | 3.4 (3.2 to 3.7)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Femoral Neck Bone Mineral Density by Visit

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Femoral Neck Bone Mineral Density by Visit |
| End point description:   |  |
| Femoral neck bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.  |  |
| Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline (of extension study) and months 12, 24, 36, 60 and 84   |  |

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 2089                | 2210                  |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 2029, 2160)                    | 2.1 (1.9 to 2.3)    | 0.8 (0.7 to 1)        |  |  |
| Month 24 (n = 1918, 2045)                    | 3.2 (3.1 to 3.4)    | 1.2 (1 to 1.4)        |  |  |
| Month 36 (n = 1475, 1591)                    | 4 (3.8 to 4.3)      | 1.7 (1.5 to 1.9)      |  |  |
| Month 60 (n = 1439, 1538)                    | 5.7 (5.4 to 5.9)    | 2.8 (2.6 to 3.1)      |  |  |
| Month 84 (n = 1200, 1232)                    | 7.1 (6.8 to 7.4)    | 3.8 (3.5 to 4.2)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in 1/3 Radius Bone Mineral Density by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in 1/3 Radius Bone Mineral Density by Visit |
|-----------------|--|

End point description:

1/3 radius bone mineral density was measured in a subset of participants by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants in the DXA substudy with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

End point timeframe:

Baseline (of extension study) and months 12, 24, 36, 60 and 84

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 449                 | 467                   |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 114, 134)                      | 0.3 (-0.2 to 0.9)   | 0.6 (0.1 to 1.2)      |  |  |
| Month 24 (n = 108, 127)                      | 0.2 (-0.4 to 0.9)   | 0.2 (-0.4 to 0.8)     |  |  |
| Month 36 (n = 73, 93)                        | 1.3 (0.5 to 2)      | 0.6 (-0.1 to 1.3)     |  |  |
| Month 60 (n = 59, 84)                        | 1.8 (0.9 to 2.7)    | 1.4 (0.6 to 2.2)      |  |  |
| Month 84 (n = 39, 56)                        | 2.2 (0.9 to 3.6)    | 1 (-0.1 to 2.2)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Study 20030216 Baseline in Lumbar Spine Bone Mineral Density by Visit

|                 |   |
|-----------------|---|
| End point title | Percent Change From Study 20030216 Baseline in Lumbar Spine Bone Mineral Density by Visit |
|-----------------|---|

**End point description:**

Lumbar spine bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

**End point timeframe:**

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

| <b>End point values</b>                      | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|--|------------------------|--------------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed                  | 2089                   | 2210                     |  |  |
| Units: percent change                        |                        |                          |  |  |
| least squares mean (confidence interval 95%) |                        |                          |  |  |
| Month 12 (n = 2030, 2148)                    | 5.9 (5.6 to 6.1)       | 11.9 (11.7 to 12.2)      |  |  |
| Month 24 (n = 1924, 2041)                    | 8.4 (8.1 to 8.7)       | 13.7 (13.4 to 13.9)      |  |  |
| Month 36 (n = 1487, 1589)                    | 10.1 (9.8 to 10.4)     | 15.2 (14.9 to 15.5)      |  |  |
| Month 60 (n = 1464, 1551)                    | 13.8 (13.4 to 14.1)    | 18.4 (18.1 to 18.8)      |  |  |
| Month 84 (n = 1216, 1251)                    | 17.3 (16.8 to 17.8)    | 21.7 (21.2 to 22.2)      |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percent Change From Study 20030216 Baseline in Total Hip BMD by Visit**

|                 |   |
|-----------------|---|
| End point title | Percent Change From Study 20030216 Baseline in Total Hip BMD by Visit |
|-----------------|---|

**End point description:**

Total hip bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center. M

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

**End point timeframe:**

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 2089                | 2210                  |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 2006, 2132)                    | 1.7 (1.6 to 1.9)    | 6.4 (6.3 to 6.6)      |  |  |
| Month 24 (n = 1895, 2017)                    | 2.9 (2.7 to 3)      | 7.1 (6.9 to 7.2)      |  |  |
| Month 36 (n = 1457, 1567)                    | 3.6 (3.4 to 3.8)    | 7.5 (7.3 to 7.7)      |  |  |
| Month 60 (n = 1424, 1518)                    | 4.9 (4.7 to 5.2)    | 8.4 (8.1 to 8.6)      |  |  |
| Month 84 (n = 1189, 1215)                    | 6.1 (5.8 to 6.4)    | 9.2 (8.9 to 9.5)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Study 20030216 Baseline in Femoral Neck BMD by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Study 20030216 Baseline in Femoral Neck BMD by Visit |
|-----------------|--|

End point description:

Femoral neck bone mineral density was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60 and 84

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 2089                | 2210                  |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 2006, 2132)                    | 1.4 (1.2 to 1.7)    | 5.8 (5.6 to 6)        |  |  |
| Month 24 (n = 1895, 2017)                    | 2.6 (2.3 to 2.8)    | 6.2 (6 to 6.5)        |  |  |
| Month 36 (n = 1457, 1567)                    | 3.4 (3.1 to 3.6)    | 6.7 (6.5 to 7)        |  |  |
| Month 60 (n = 1424, 1518)                    | 5 (4.7 to 5.3)      | 7.9 (7.6 to 8.2)      |  |  |
| Month 84 (n = 1189, 1215)                    | 6.4 (6 to 6.8)      | 9 (8.6 to 9.4)        |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percent Change From Study 20030216 Baseline in 1/3 Radius BMD by Visit**

|                 |  |
|-----------------|--|
| End point title | Percent Change From Study 20030216 Baseline in 1/3 Radius BMD by Visit |
|-----------------|--|

End point description:

1/3 radius BMD was measured by dual x-ray absorptiometry (DXA). DXA scans were analyzed by a central imaging center.

Analysis includes participants in the DXA substudy with an Extension Study baseline and at least 1 post-baseline DXA BMD measurement. "n" indicates the number of participants with available data at each time point.

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

End point timeframe:

Study 20030216 baseline and extension study months 12, 24, 36, 60, and 84

| End point values                             | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                  | 449                 | 467                   |  |  |
| Units: percent change                        |                     |                       |  |  |
| least squares mean (confidence interval 95%) |                     |                       |  |  |
| Month 12 (n = 113, 133)                      | -1 (-1.7 to -0.3)   | 2.6 (1.9 to 3.2)      |  |  |
| Month 24 (n = 107, 127)                      | -1.2 (-1.9 to -0.4) | 2.1 (1.4 to 2.8)      |  |  |
| Month 36 (n = 73, 92)                        | -0.2 (-1.1 to 0.7)  | 2.4 (1.6 to 3.2)      |  |  |
| Month 60 (n = 59, 83)                        | 0.3 (-0.7 to 1.3)   | 3.3 (2.4 to 4.2)      |  |  |
| Month 84 (n = 39, 56)                        | 0.6 (-0.8 to 2.1)   | 2.8 (1.6 to 4.1)      |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Participants With New Vertebral Fractures**

|                 |   |
|-----------------|---|
| End point title | Number of Participants With New Vertebral Fractures |
|-----------------|---|

End point description:

A new vertebral fracture, assessed by lateral spine X-ray using Genant semiquantitative scoring method, was identified as an  $\geq 1$  grade increase from the previous grade of 0 in any vertebra from T4 to L4, excluding any fracture associated with high trauma severity or a pathologic fracture.

Analysis includes all participants enrolled in the extension study who have vertebral X-ray assessment at the extension baseline and at least 1 post-extension baseline visit.

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

End point timeframe:

84 months

| End point values            | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|-----------------------------|---------------------|-----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed | 1991                | 2116                  |  |  |
| Units: participants         |                     |                       |  |  |
| number (not applicable)     | 145                 | 149                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Non-Vertebral Fractures

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Non-Vertebral Fractures |
|-----------------|---|

End point description:

Non-vertebral fractures (osteoporotic) were defined as a fracture present on a copy of radiographs or other diagnostic images such as computerized tomography (CT) or magnetic resonance imaging (MRI) confirming the fracture, and/or documented in a copy of the radiology report, surgical report, or discharge summary, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity or pathologic fractures were excluded.

Analysis includes all enrolled participants.

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

End point timeframe:

84 months

| End point values            | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|-----------------------------|---------------------|-----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed | 2207                | 2343                  |  |  |
| Units: participants         |                     |                       |  |  |
| number (not applicable)     | 219                 | 172                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in C-Telopeptide 1 (CTX-1) by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in C-Telopeptide 1 (CTX-1) by Visit |
|-----------------|--|

End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

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

End point timeframe:

Baseline (of extension study), day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

| <b>End point values</b>               | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|---------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed           | 318                    | 342                      |  |  |
| Units: percent change                 |                        |                          |  |  |
| median (inter-quartile range (Q1-Q3)) |                        |                          |  |  |
| Day 10 (n = 26, 47)                   | -90 (-93 to -85)       | -72 (-86 to -47)         |  |  |
| Month 6 (n = 30, 56)                  | -85 (-91 to -73)       | -26 (-63 to 1)           |  |  |
| Month 12 (n = 27, 56)                 | -75 (-90 to -54)       | -13 (-37 to 24)          |  |  |
| Month 24 (n = 27, 47)                 | -67 (-84 to -29)       | 10 (-27 to 55)           |  |  |
| Month 36 (n = 68, 81)                 | -59 (-84 to -28)       | 2 (-32 to 68)            |  |  |
| Month 48 (n = 62, 75)                 | -58 (-84 to -12)       | 0 (-46 to 56)            |  |  |
| Month 60 (n = 59, 70)                 | -65 (-90 to -19)       | 0 (-47 to 83)            |  |  |
| Month 72 (n = 56, 62)                 | -60 (-85 to -16)       | -1 (-47 to 76)           |  |  |
| Month 84 (n = 41, 41)                 | -64 (-86 to -28)       | -6 (-26 to 68)           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline in Procollagen Type 1 N-telopeptide (P1NP) by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Procollagen Type 1 N-telopeptide (P1NP) by Visit |
|-----------------|--|

End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

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

End point timeframe:

Baseline (of extension study), day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

| End point values                      | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed           | 318                 | 342                   |  |  |
| Units: percent change                 |                     |                       |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                       |  |  |
| Day 10 (n = 30, 51)                   | 6 (-5 to 30)        | 14 (-1 to 25)         |  |  |
| Month 6 (n = 30, 53)                  | -71 (-78 to -62)    | -23 (-50 to -2)       |  |  |
| Month 12 (n = 26, 56)                 | -67 (-76 to -57)    | 7 (-15 to 30)         |  |  |
| Month 24 (n = 27, 47)                 | -63 (-77 to -41)    | 11 (-17 to 42)        |  |  |
| Month 36 (n = 69, 83)                 | -57 (-67 to -29)    | 29 (-6 to 91)         |  |  |
| Month 48 (n = 61, 73)                 | -60 (-70 to -41)    | 8 (-21 to 49)         |  |  |
| Month 60 (n = 61, 71)                 | -54 (-72 to -35)    | 30 (-6 to 67)         |  |  |
| Month 72 (n = 55, 64)                 | -50 (-60 to -36)    | 44 (3 to 103)         |  |  |
| Month 84 (n = 48, 50)                 | -59 (-73 to -40)    | 32 (-4 to 75)         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Study 20030216 Baseline in CTX-1 by Visit

|  |   |
|--|---|
| End point title  | Percent Change From Study 20030216 Baseline in CTX-1 by Visit |
| End point description:   |   |
| Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Study 20030216 Baseline and extension study day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84   |   |

| End point values                      | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed           | 318                 | 342                   |  |  |
| Units: percent change                 |                     |                       |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                       |  |  |
| Day 10 (n = 26, 56)                   | -90 (-91 to -78)    | -91 (-93 to -86)      |  |  |
| Month 6 (n = 32, 72)                  | -83 (-90 to -72)    | -77 (-87 to -49)      |  |  |
| Month 12 (n = 27, 65)                 | -77 (-91 to -45)    | -63 (-87 to -11)      |  |  |

|                         |                  |                  |  |  |
|-------------------------|------------------|------------------|--|--|
| Month 24 (n = 28, 60)   | -65 (-80 to -24) | -53 (-82 to 0)   |  |  |
| Month 36 (n = 289, 313) | -71 (-88 to -40) | -52 (-86 to -4)  |  |  |
| Month 48 (n = 274, 290) | -70 (-88 to -36) | -61 (-85 to -24) |  |  |
| Month 60 (n = 268, 276) | -67 (-88 to -25) | -53 (-86 to -18) |  |  |
| Month 72 (n = 243, 248) | -69 (-88 to -32) | -59 (-86 to -21) |  |  |
| Month 84 (n = 217, 216) | -63 (-88 to -19) | -53 (-84 to -12) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Study 20030216 Baseline in P1NP by Visit

|                 |  |
|-----------------|--|
| End point title | Percent Change From Study 20030216 Baseline in P1NP by Visit |
|-----------------|--|

End point description:

Bone turnover markers were collected in a subset of participants who participated in the 20030216 Bone Marker sub-study and in new participants continuing beyond month 24 who were not previously in the Bone Turnover Markers sub-study.

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

End point timeframe:

Study 20030216 Baseline and extension study day 10, and months 6, 12, 24, 36, 48, 60, 72, and 84

| End point values                      | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed           | 318                 | 342                   |  |  |
| Units: percent change                 |                     |                       |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                       |  |  |
| Day 10 (n = 30, 51)                   | 9 (-14 to 34)       | -59 (-74 to -22)      |  |  |
| Month 6 (n = 32, 57)                  | -74 (-80 to -67)    | -75 (-80 to -55)      |  |  |
| Month 12 (n = 26, 56)                 | -74 (-79 to -51)    | -63 (-76 to -36)      |  |  |
| Month 24 (n = 28, 51)                 | -67 (-75 to -51)    | -56 (-72 to -30)      |  |  |
| Month 36 (n = 70, 83)                 | -59 (-75 to -37)    | -60 (-71 to -40)      |  |  |
| Month 48 (n = 61, 73)                 | -67 (-75 to -46)    | -63 (-77 to -42)      |  |  |
| Month 60 (n = 61, 71)                 | -62 (-75 to -42)    | -55 (-74 to -30)      |  |  |
| Month 72 (n = 56, 67)                 | -62 (-71 to -35)    | -55 (-70 to -27)      |  |  |
| Month 84 (n = 49, 53)                 | -68 (-78 to -56)    | -57 (-74 to -38)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Albumin-adjusted Serum Calcium at Day 10

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Albumin-adjusted Serum Calcium at Day 10 |
|-----------------|--|

End point description:

Analysis includes participants who had a calcium corrected by albumin measurement within the Day 10 visit window up to May 31, 2008.

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

End point timeframe:

Baseline (of extension study) and day 10

| End point values                      | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed           | 2027                | 2154                  |  |  |
| Units: percent change                 |                     |                       |  |  |
| median (inter-quartile range (Q1-Q3)) | -3.1 (-6.1 to 0)    | -2 (-5.1 to 1.1)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Serum Denosumab Concentration

|                 |                               |
|-----------------|-------------------------------|
| End point title | Serum Denosumab Concentration |
|-----------------|-------------------------------|

End point description:

Serum concentrations of denosumab were measured by a validated conventional sandwich enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) was 0.8 ng/mL. Values of 0 in the table below indicate data below the lower limit of quantification.

Analysis includes participants who participated in the Study 20030216 PK substudy, for whom dosing information was not missing and for whom sampling was within 14 days of specified sampling times.

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

End point timeframe:

Baseline (pre-dose in extension study), day 10, and Months 3, 4 and 6 (pre-dose)

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 97                  | 113                   |  |  |
| Units: ng/mL                         |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Baseline (n = 97, 113)               | 0 (± 0)             | 113 (± 107)           |  |  |
| Day 10 (n = 92, 106)                 | 5890 (± 2010)       | 6010 (± 2530)         |  |  |
| Month 3 (n = 81, 92)                 | 1000 (± 560)        | 1190 (± 690)          |  |  |
| Month 4 (n = 87, 104)                | 429 (± 378)         | 554 (± 480)           |  |  |
| Month 6 (n = 87, 103)                | 20.8 (± 61.7)       | 66 (± 147.2)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Cancellous Bone Volume

|  |   |
|--|---|
| End point title  | Bone Histomorphometry: Cancellous Bone Volume |
| End point description:   |   |
| <p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cancellous (trabecular) bone volume is the percent of the total marrow cavity that is occupied by cancellous bone (both mineralized and non-mineralized) measured by quantitative histomorphometry. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cancellous bone volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p> |   |
| End point type   | Secondary                                     |
| End point timeframe:   |   |
| Month 24 and month 84  |   |

| End point values                              | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---|---------------------|-----------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                   | 13                  | 41                    |  |  |
| Units: percentage of total bone tissue volume |                     |                       |  |  |
| arithmetic mean (standard deviation)          |                     |                       |  |  |
| Month 24 (n=13, 25)                           | 15.253 (± 6.065)    | 14.64 (± 6.979)       |  |  |
| Month 84 (n=0, 19)                            | 99999 (± 99999)     | 16.358 (± 4.438)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Trabecular Number

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Trabecular Number |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Trabecular number is the number of trabeculae present per lineal mm and is calculated as trabecular bone volume/trabecular thickness. Trabecular number is a measure of trabecular connectivity and decreases with bone loss.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: 1/mm                          |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 1.005 (± 0.242)     | 0.904 (± 0.243)       |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 1.235 (± 0.254)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Trabecular Separation

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Trabecular Separation |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Trabecular separation is the mean distance between trabeculae (measured by integrated computer graphics). Trabecular separation increases with trabecular bone loss.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular separation data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab      | Denosumab / Denosumab     |  |  |
|--------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group           |  |  |
| Number of subjects analysed          | 13                       | 41                        |  |  |
| Units: $\mu\text{m}$                 |                          |                           |  |  |
| arithmetic mean (standard deviation) |                          |                           |  |  |
| Month 24 (n = 13, 25)                | 919.693 ( $\pm$ 358.238) | 1033.416 ( $\pm$ 352.259) |  |  |
| Month 84 (n = 0, 19)                 | 99999 ( $\pm$ 99999)     | 708.669 ( $\pm$ 171.782)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Trabecular Thickness

|  |   |
|--|---|
| End point title  | Bone Histomorphometry: Trabecular Thickness |
| End point description:   |   |
| <p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Mean trabecular thickness is a measure of trabecular structure and is calculated as the reciprocal of total bone (trabecular) surfaces. Trabecular thickness is reduced by aging and osteoporosis.</p> <p>The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available trabecular thickness data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p> |   |
| End point type   | Secondary                                   |
| End point timeframe:   |   |
| Month 24 and month 84  |   |

| End point values                     | Placebo / Denosumab     | Denosumab / Denosumab   |  |  |
|--------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group         |  |  |
| Number of subjects analysed          | 13                      | 41                      |  |  |
| Units: $\mu\text{m}$                 |                         |                         |  |  |
| arithmetic mean (standard deviation) |                         |                         |  |  |
| Month 24 (n = 13, 25)                | 153.878 ( $\pm$ 51.859) | 156.335 ( $\pm$ 48.567) |  |  |
| Month 84 (n = 0, 19)                 | 99999 ( $\pm$ 99999)    | 132.965 ( $\pm$ 28.064) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Cortical Width

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Bone Histomorphometry: Cortical Width |
|-----------------|---------------------------------------|

---

**End point description:**

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cortical width is the average width of both inner and outer cortices. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cortical width data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

---

End point timeframe:

Month 24 and month 84

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| End point values                     | Placebo / Denosumab   | Denosumab / Denosumab  |  |  |
|--------------------------------------|-----------------------|------------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group        |  |  |
| Number of subjects analysed          | 13                    | 45                     |  |  |
| Units: $\mu\text{m}$                 |                       |                        |  |  |
| arithmetic mean (standard deviation) |                       |                        |  |  |
| Month 24 (n = 13, 28)                | 622.22 ( $\pm$ 246.7) | 707.69 ( $\pm$ 237.97) |  |  |
| Month 84 (n = 0, 21)                 | 99999 ( $\pm$ 99999)  | 786.19 ( $\pm$ 279.81) |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Bone Histomorphometry: Cancellous Bone Volume by TRAP Histomorphometry**

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|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Cancellous Bone Volume by TRAP Histomorphometry |
|-----------------|--|

---

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Cancellous (trabecular) bone volume is the percent of the total marrow cavity that is occupied by cancellous bone (both mineralized and non-mineralized) measured by tartrate-resistant acid phosphatase (TRAP) staining histomorphometry.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available cancellous bone volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

---

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

---

End point timeframe:

Month 24 and month 84

---

| End point values                              | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---|---------------------|-----------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed                   | 13                  | 41                    |  |  |
| Units: percentage of total bone tissue volume |                     |                       |  |  |
| arithmetic mean (standard deviation)          |                     |                       |  |  |
| Month 24 (n = 13, 25)                         | 16.678 (± 7.27)     | 15.606 (± 6.986)      |  |  |
| Month 84 (n = 0, 19)                          | 99999 (± 99999)     | 17.631 (± 4.387)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Surface Density

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Surface Density |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Surface density is calculated by total bone (trabecular) surfaces / total tissue volume. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available surface density data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                        | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---|---------------------|-----------------------|--|--|
| Subject group type                      | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed             | 13                  | 41                    |  |  |
| Units: mm <sup>2</sup> /mm <sup>3</sup> |                     |                       |  |  |
| arithmetic mean (standard deviation)    |                     |                       |  |  |
| Month 24 (n = 13, 25)                   | 2.009 (± 0.486)     | 1.807 (± 0.486)       |  |  |
| Month 84 (n = 0, 19)                    | 99999 (± 99999)     | 2.472 (± 0.506)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Osteoblast - Osteoid Interface

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Osteoblast - Osteoid Interface |
|-----------------|---|

**End point description:**

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoblast - osteoid interface is calculated as osteoblast surface / osteoid surface \* 100. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoblast - osteoid interface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

**End point timeframe:**

Month 24 and month 84

| <b>End point values</b>              | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: percentage of osteoid surface |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 22.124 (± 34.879)   | 17.813 (± 28.381)     |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 5.951 (± 15.223)      |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Bone Histomorphometry: Osteoid Surface**

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Osteoid Surface |
|-----------------|--|

**End point description:**

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid surface is the percent of bone surface covered in osteoid. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

**End point timeframe:**

Month 24 and month 84

| <b>End point values</b>                 | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|---|---------------------|-----------------------|--|--|
| Subject group type                      | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed             | 13                  | 41                    |  |  |
| Units: percentage of total bone surface |                     |                       |  |  |
| arithmetic mean (standard deviation)    |                     |                       |  |  |

|                       |                 |                 |  |  |
|-----------------------|-----------------|-----------------|--|--|
| Month 24 (n = 13, 25) | 0.915 (± 1.382) | 0.982 (± 2.489) |  |  |
| Month 84 (n = 0, 19)  | 99999 (± 99999) | 0.421 (± 1.068) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Osteoid Thickness

|   |  |
|---|--|
| End point title   | Bone Histomorphometry: Osteoid Thickness |
| End point description:  |  |
| <p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid thickness (width) is the mean thickness of osteoid seams on cancellous surfaces. Osteoid thickness is normally &lt;12.5 µm. Increased osteoid thickness suggests abnormal mineralization (osteomalacia).</p> <p>The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid thickness data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p> |  |
| End point type  | Secondary                                |
| End point timeframe:  |  |
| Month 24 and month 84   |  |

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: µm                            |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 5.139 (± 3.261)     | 4.548 (± 4.973)       |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 4.108 (± 3.476)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Wall Thickness

|   |                                       |
|---|---------------------------------------|
| End point title   | Bone Histomorphometry: Wall Thickness |
| End point description:  |                                       |
| <p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Wall thickness is the average thickness of trabecular bone structural units (BSU) and is used to assess the overall balance between resorption and formation.</p> <p>The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available wall thickness data. Biopsies were only</p> |                                       |

collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Month 24 and month 84 |           |

| End point values                     | Placebo / Denosumab  | Denosumab / Denosumab |  |  |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed          | 13                   | 41                    |  |  |
| Units: $\mu\text{m}$                 |                      |                       |  |  |
| arithmetic mean (standard deviation) |                      |                       |  |  |
| Month 24 (n = 13, 25)                | 43.11 ( $\pm$ 6.08)  | 49.74 ( $\pm$ 10.51)  |  |  |
| Month 84 (n = 0, 19)                 | 99999 ( $\pm$ 99999) | 39.59 ( $\pm$ 7.49)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Eroded Surface/Bone Surface

|  |  |
|--|--|
| End point title  | Bone Histomorphometry: Eroded Surface/Bone Surface |
| End point description:   |  |
| <p>Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Eroded surface/bone surface is the percentage of bone surface occupied by eroded (resorption) cavities (Howships lacunae), with or without osteoclasts.</p> <p>The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available eroded surface/bone surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.</p> |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Month 24 and month 84  |  |

| End point values                     | Placebo / Denosumab  | Denosumab / Denosumab |  |  |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed          | 13                   | 41                    |  |  |
| Units: percentage of bone surface    |                      |                       |  |  |
| arithmetic mean (standard deviation) |                      |                       |  |  |
| Month 24 (n = 13, 25)                | 0.414 ( $\pm$ 0.701) | 0.328 ( $\pm$ 0.613)  |  |  |
| Month 84 (n = 0, 19)                 | 99999 ( $\pm$ 99999) | 0.511 ( $\pm$ 0.579)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Osteoclast Number - Length Based

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Osteoclast Number - Length Based |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured by quantitative histomorphometry and is expressed per mm of bone. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|--------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed          | 13                     | 41                       |  |  |
| Units: 1/mm                          |                        |                          |  |  |
| arithmetic mean (standard deviation) |                        |                          |  |  |
| Month 24 (n = 13, 25)                | 0.086 (±<br>0.119)     | 0.107 (±<br>0.198)       |  |  |
| Month 84 (n = 0, 19)                 | 99999 (±<br>99999)     | 0.074 (±<br>0.101)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Osteoclast Number - Surface Based

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Osteoclast Number - Surface Based |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured by quantitative histomorphometry and is expressed per 100 mm of bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Month 24 and month 84 |           |

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: 1/100 mm                      |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 8.6 (± 11.9)        | 10.7 (± 19.8)         |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 7.4 (± 10.1)          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Osteoclast Number by TRAP - Length Based

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Osteoclast Number by TRAP - Length Based |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured using TRAP staining and is expressed per mm of bone.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Month 24 and month 84 |           |

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: 1/mm                          |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 0.096 (± 0.134)     | 0.11 (± 0.185)        |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 0.077 (± 0.107)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Osteoclast Number by TRAP - Surface Based

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Osteoclast Number by TRAP - Surface Based |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoclast number was measured using TRAP staining and is expressed per 100 mm of bone surface. The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoclast number data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 13                  | 41                    |  |  |
| Units: 1/100 mm                      |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 13, 25)                | 9.6 (± 13.4)        | 11 (± 18.5)           |  |  |
| Month 84 (n = 0, 19)                 | 99999 (± 99999)     | 7.7 (± 10.7)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Single-label Surface

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Single-label Surface |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. A single label is deposited if formation either started or ended during the interval between the uses of the two courses of tetracycline administration. Single-label surface is expressed as a percentage of total bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available single-label surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|--------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed          | 5                      | 20                       |  |  |
| Units: percentage of bone surface    |                        |                          |  |  |
| arithmetic mean (standard deviation) |                        |                          |  |  |
| Month 24 (n = 5, 10)                 | 0.304 (±<br>0.302)     | 0.643 (±<br>0.661)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (±<br>99999)     | 0.611 (±<br>0.726)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Double-label Surface

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Double-label Surface |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The presence of double labels indicates that normal bone mineralization was actively occurring over the entire labeling interval. Double-label surface is expressed as a percentage of total bone surface.

The analysis includes Participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available double-label surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|--------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed          | 5                      | 20                       |  |  |
| Units: percentage of bone surface    |                        |                          |  |  |
| arithmetic mean (standard deviation) |                        |                          |  |  |
| Month 24 (n = 5, 10)                 | 0.258 (±<br>0.207)     | 0.356 (±<br>0.295)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (±<br>99999)     | 0.106 (±<br>0.237)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Mineralizing Surface

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Mineralizing Surface |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Total mineralizing surfaces (MS) include all double and half of single-labeled surfaces. MS is expressed as a percentage of total bone surface.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineralizing surface data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 5                   | 20                    |  |  |
| Units: percentage of bone surface    |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 5, 10)                 | 0.406 (± 0.323)     | 0.681 (± 0.453)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (± 99999)     | 0.412 (± 0.458)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Mineral Apposition Rate

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Mineral Apposition Rate |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The mineral apposition rate (MAR) is the average rate at which new bone mineral is being added on any actively forming surface. MAR is calculated as the average distance between visible labels, divided by the labeling interval.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineral apposition rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 5                   | 20                    |  |  |
| Units: µm/day                        |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 5, 10)                 | 0.616 (± 0.219)     | 0.722 (± 0.573)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (± 99999)     | 0.394 (± 0.233)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Adjusted Apposition Rate

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Adjusted Apposition Rate |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. MAR is the average rate at which new bone mineral is being added on any actively forming surface. Adjusted MAR is calculated as: (average distance between visible labels / labeling interval) \* (total mineralizing surface/total bone surface).

Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or 84 and with available adjusted apposition rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 5                   | 19                    |  |  |
| Units: µm/day                        |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 5, 9)                  | 0.394 (± 0.471)     | 0.517 (± 0.537)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (± 99999)     | 0.818 (± 1.207)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Bone Formation Rate - Surface Based

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Bone Formation Rate - Surface Based |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Bone formation rate - surface based is the calculated rate at which cancellous bone surface is being replaced annually, derived from the Mineral Appositional Rate \* 365 \* (relative mineralizing surface / total bone surface).

The analysis included participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available bone formation rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                                 | Placebo / Denosumab  | Denosumab / Denosumab |  |  |
|--|----------------------|-----------------------|--|--|
| Subject group type                               | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed                      | 5                    | 20                    |  |  |
| Units: $\mu\text{m}^3/\mu\text{m}^2/\text{year}$ |                      |                       |  |  |
| arithmetic mean (standard deviation)             |                      |                       |  |  |
| Month 24 (n = 5, 10)                             | 0.898 ( $\pm$ 0.706) | 2.153 ( $\pm$ 2.468)  |  |  |
| Month 84 (n = 0, 10)                             | 99999 ( $\pm$ 99999) | 0.691 ( $\pm$ 0.868)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Bone Formation Rate - Volume Based

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Bone Formation Rate - Volume Based |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Bone formation rate - volume based is the calculated rate at which cancellous bone volume is being replaced annually, derived from the Mineral Appositional Rate \* 365 \* (relative mineralizing surface / total bone volume).

The analyses includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available bone formation rate data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:  
Month 24 and month 84

| End point values                       | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                     | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed            | 5                   | 20                    |  |  |
| Units: percent of bone volume per year |                     |                       |  |  |
| arithmetic mean (standard deviation)   |                     |                       |  |  |
| Month 24 (n = 5, 10)                   | 1.454 (± 1.265)     | 3.162 (± 3.773)       |  |  |
| Month 84 (n = 0, 10)                   | 99999 (± 99999)     | 1.071 (± 1.308)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Activation Frequency

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Activation Frequency |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. The average time that it takes for a new remodeling cycle to begin on any point on a cancellous surface is called the activation frequency. Activation frequency is calculated as the bone formation rate / wall width.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available activation frequency data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 5                   | 20                    |  |  |
| Units: /year                         |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 5, 10)                 | 0.022 (± 0.019)     | 0.045 (± 0.049)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (± 99999)     | 0.014 (± 0.024)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Formation Period

|                 |   |
|-----------------|---|
| End point title | Bone Histomorphometry: Formation Period |
|-----------------|---|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Formation period (FP) is the mean time required to rebuild a new bone structural unit or osteon from the cement line back to the bone surface at a single location, and is given by wall width / adjusted apposition rate.

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available formation period data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

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

End point timeframe:

Month 24 and month 84

| End point values                     | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|--------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed          | 5                      | 20                       |  |  |
| Units: days                          |                        |                          |  |  |
| arithmetic mean (standard deviation) |                        |                          |  |  |
| Month 24 (n = 5, 10)                 | 593.5 (±<br>996.8)     | 287.3 (±<br>391.5)       |  |  |
| Month 84 (n = 0, 10)                 | 99999 (±<br>99999)     | 229.7 (± 512)            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Histomorphometry: Osteoid Volume

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Bone Histomorphometry: Osteoid Volume |
|-----------------|---------------------------------------|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. Osteoid volume is the percentage of a given volume of bone tissue that consists of unmineralized bone (osteoid).

The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of

denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available osteoid volume data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Month 24 and month 84 |           |

| End point values                       | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--|---------------------|-----------------------|--|--|
| Subject group type                     | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed            | 13                  | 41                    |  |  |
| Units: percentage of total bone tissue |                     |                       |  |  |
| arithmetic mean (standard deviation)   |                     |                       |  |  |
| Month 24 (n = 13, 25)                  | 0.108 (± 0.193)     | 0.146 (± 0.382)       |  |  |
| Month 84 (n = 0, 19)                   | 99999 (± 99999)     | 0.048 (± 0.133)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histomorphometry: Mineralization Lag Time

|                 |  |
|-----------------|--|
| End point title | Bone Histomorphometry: Mineralization Lag Time |
|-----------------|--|

End point description:

Bone biopsy samples were prepared according to standard procedures for bone histomorphometry. A double tetracycline labeling procedure was used to allow visualization and quantification of sites of new bone formation. Tetracycline was given for two periods of 3 days separated by 14 days where no tetracycline was taken. Mineralization lag time is the average time interval between osteoid formation and its subsequent mineralization and is calculated by dividing the osteoid width by the apposition rate. The analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, had at least 1 bone biopsy evaluable for histomorphometry at extension month 24 or extension month 84 and with available mineralization lag time data. Biopsies were only collected from participants in the Denosumab/Denosumab group at month 84; "99999" indicates data not available.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Month 24 and month 84 |           |

| End point values                     | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|--------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed          | 5                   | 20                    |  |  |
| Units: days                          |                     |                       |  |  |
| arithmetic mean (standard deviation) |                     |                       |  |  |
| Month 24 (n = 5, 10)                 | 84.9 (± 136.8)      | 54.3 (± 76.1)         |  |  |

|                      |                 |                |  |  |
|----------------------|-----------------|----------------|--|--|
| Month 84 (n = 0, 10) | 99999 (± 99999) | 52.3 (± 114.5) |  |  |
|----------------------|-----------------|----------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histology at Month 24

|   |                            |
|---|----------------------------|
| End point title   | Bone Histology at Month 24 |
| End point description:  |                            |
| Bone biopsy samples were prepared according to standard procedures for bone histology to determine if there were any histological abnormalities in the bone. Results are reported for the number of biopsies with normal bone micro-architecture: normal lamellar bone, normal mineralization, and osteoid, and biopsies with abnormal bone histology: osteomalacia, marrow fibrosis, or woven bone. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, and had at least 1 evaluable bone biopsy at extension month 24. |                            |
| End point type  | Secondary                  |
| End point timeframe:  |                            |
| Month 24  |                            |

| End point values            | Placebo / Denosumab | Denosumab / Denosumab |  |  |
|-----------------------------|---------------------|-----------------------|--|--|
| Subject group type          | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed | 13                  | 28                    |  |  |
| Units: biopsies             |                     |                       |  |  |
| Normal lamellar bone        | 13                  | 28                    |  |  |
| Normal mineralization       | 13                  | 28                    |  |  |
| Osteoid                     | 13                  | 23                    |  |  |
| Osteomalacia                | 0                   | 0                     |  |  |
| Marrow fibrosis             | 0                   | 0                     |  |  |
| Woven bone                  | 0                   | 0                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bone Histology at Month 84

|   |                            |
|---|----------------------------|
| End point title   | Bone Histology at Month 84 |
| End point description:  |                            |
| Bone biopsy samples were prepared according to standard procedures for bone histology to determine if there were any histological abnormalities in the bone. Results are reported for the number of biopsies with normal bone micro-architecture: normal lamellar bone, normal mineralization, and osteoid, and biopsies with abnormal bone histology: osteomalacia, marrow fibrosis, or woven bone. Analysis includes participants who enrolled in the bone biopsy substudy, received at least 1 dose of denosumab during the extension study, and had at least 1 evaluable bone biopsy at extension month |                            |

84.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Month 84             |           |

| End point values            | Placebo /<br>Denosumab | Denosumab /<br>Denosumab |  |  |
|-----------------------------|------------------------|--------------------------|--|--|
| Subject group type          | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed | 0 <sup>[4]</sup>       | 22                       |  |  |
| Units: biopsies             |                        |                          |  |  |
| Normal lamellar bone        |                        | 22                       |  |  |
| Normal mineralization       |                        | 22                       |  |  |
| Osteoid                     |                        | 18                       |  |  |
| Osteomalacia                |                        | 0                        |  |  |
| Marrow fibrosis             |                        | 0                        |  |  |
| Woven bone                  |                        | 0                        |  |  |

Notes:

[4] - No participants had biopsies collected at month 84

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

84 Months

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

### Dictionary used

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

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

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Placebo/Denosumab 60 mg Q6M |
|-----------------------|-----------------------------|

Reporting group description:

Participants who were randomized to placebo in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Denosumab/Denosumab 60 mg Q6M |
|-----------------------|-------------------------------|

Reporting group description:

Participants who were randomized to denosumab in the core study received a 60 mg subcutaneous injection of denosumab every 6 months for up to seven years in the extension study (total of 10 years treatment).

| Serious adverse events  | Placebo/Denosumab<br>60 mg Q6M | Denosumab/Denosu<br>mab 60 mg Q6M |  |
|---|--------------------------------|-----------------------------------|--|
| Total subjects affected by serious adverse events                   |                                |                                   |  |
| subjects affected / exposed   | 945 / 2206<br>(42.84%)         | 1014 / 2343<br>(43.28%)           |  |
| number of deaths (all causes)                                       | 101                            | 108                               |  |
| number of deaths resulting from adverse events                      |                                |                                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                |                                   |  |
| Acute myeloid leukaemia   |                                |                                   |  |
| subjects affected / exposed   | 1 / 2206 (0.05%)               | 1 / 2343 (0.04%)                  |  |
| occurrences causally related to treatment / all                     | 0 / 1                          | 0 / 1                             |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 1                             |  |
| Adenocarcinoma  |                                |                                   |  |
| subjects affected / exposed   | 1 / 2206 (0.05%)               | 1 / 2343 (0.04%)                  |  |
| occurrences causally related to treatment / all                     | 0 / 1                          | 0 / 1                             |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                             |  |
| Adenocarcinoma of colon   |                                |                                   |  |
| subjects affected / exposed   | 4 / 2206 (0.18%)               | 5 / 2343 (0.21%)                  |  |
| occurrences causally related to treatment / all                     | 0 / 4                          | 0 / 5                             |  |
| deaths causally related to treatment / all                          | 0 / 0                          | 0 / 0                             |  |
| Adenocarcinoma pancreas   |                                |                                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenoma benign                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adrenal adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenosquamous cell lung cancer                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adrenal neoplasm                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal cancer                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell lymphoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign breast neoplasm                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 16 / 2206 (0.73%) | 14 / 2343 (0.60%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign hepatic neoplasm                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign lung neoplasm                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign gastrointestinal neoplasm                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign neoplasm of bladder                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign neoplasm                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign neoplasm of thyroid gland                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign pancreatic neoplasm                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign neoplasm of skin                         |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign salivary gland neoplasm                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Benign vulval neoplasm                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bladder cancer                                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Brain cancer metastatic                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Brain neoplasm malignant                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast cancer metastatic                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast cancer                                   |                   |                   |  |
| subjects affected / exposed                     | 21 / 2206 (0.95%) | 24 / 2343 (1.02%) |  |
| occurrences causally related to treatment / all | 0 / 21            | 1 / 26            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Bronchial carcinoma                             |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Breast cancer recurrent                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carcinoma in situ of skin                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervix carcinoma                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Central nervous system lymphoma                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangiocarcinoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholesteatoma                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic lymphocytic leukaemia                   |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Colon adenoma                                   |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Colon cancer                                    |                  |                   |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%) | 12 / 2343 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3             |  |
| Colon cancer metastatic                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1             |  |
| Colon neoplasm                                  |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Colorectal cancer                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dermatofibrosarcoma protuberans                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Colorectal adenocarcinoma                       |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Diffuse large B-cell lymphoma                   |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma stage IV          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Follicular thyroid cancer                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial cancer                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal stromal tumour                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Gallbladder cancer                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal tract adenoma                  |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Gingival cancer                                 |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hairy cell leukaemia                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatic cancer                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Hepatic neoplasm                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intraductal proliferative breast lesion         |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatocellular carcinoma                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Invasive ductal breast carcinoma                |                   |                  |  |
| subjects affected / exposed                     | 10 / 2206 (0.45%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 1 / 11            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Invasive papillary breast carcinoma             |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive breast carcinoma                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leiomyosarcoma                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Laryngeal papilloma                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukaemia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lip neoplasm malignant stage unspecified        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lentigo maligna                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lipoma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung adenocarcinoma                             |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lung cancer metastatic                          |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             |  |
| Lung carcinoma cell type unspecified recurrent  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lung neoplasm                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lymphocytic leukaemia                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lung neoplasm malignant                         |                   |                   |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 13 / 2343 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 2             |  |
| Lung squamous cell carcinoma stage 0            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant melanoma                              |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 5 / 2343 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lymphoma  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant neoplasm of spinal cord               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant peritoneal neoplasm                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Mantle cell lymphoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningioma                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant urinary tract neoplasm                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mesothelioma                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to bone                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to central nervous system            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to peritoneum                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lymph nodes                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic carcinoma of the bladder             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastatic gastric cancer                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastasis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic neoplasm                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastatic renal cell carcinoma                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic squamous cell carcinoma              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Monoclonal gammopathy                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myeloproliferative disorder                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neoplasm malignant                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Neoplasm progression                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroma   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nodular fasciitis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-Hodgkin's lymphoma                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Non-small cell lung cancer                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-Hodgkin's lymphoma stage IV                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal squamous cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oral neoplasm                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal carcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ovarian cancer metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer stage III                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian fibroma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian epithelial cancer                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Pancreatic neoplasm                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pelvic neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parathyroid tumour benign                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papillary thyroid cancer                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plasma cell myeloma                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Phyllodes tumour                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plasmacytoma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polycythaemia vera                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenocarcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenoma                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Rectosigmoid cancer                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin cancer                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of lung                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of skin                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the oral cavity      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transitional cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tongue neoplasm malignant stage unspecified     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid cancer                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureteric cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine leiomyoma                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulval cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Accelerated hypertension                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic aneurysm                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Aortic dissection                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Arterial disorder                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 8 / 2343 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arterial haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arterial occlusive disease                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriosclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Circulatory collapse                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%) | 8 / 2343 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Embolism venous                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Essential hypertension                          |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femoral artery occlusion                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femoral artery aneurysm                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haemorrhage                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haematoma                                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertension                                    |                   |                   |  |
| subjects affected / exposed                     | 18 / 2206 (0.82%) | 21 / 2343 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 23            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypotension                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive crisis                             |                   |                   |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypovolaemic shock                              |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Intermittent claudication                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral embolism                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral venous disease                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Phlebolith                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shock haemorrhagic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian artery occlusion                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Temporal arteritis                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis superficial                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varicose vein                                   |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vasculitis                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vasculitis necrotising                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Venous thrombosis limb                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Arthrodesis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anticoagulant therapy                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign tumour excision                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac pacemaker replacement                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chemotherapy                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip arthroplasty                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hospitalisation                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hysterectomy                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint arthroplasty                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Knee arthroplasty                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal decompression                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rehabilitation therapy                          |                  |                  |  |

|  |                   |                   |  |
|--|-------------------|-------------------|--|
| subjects affected / exposed                          | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Urethral operation                                   |                   |                   |  |
| subjects affected / exposed                          | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Tooth extraction                                     |                   |                   |  |
| subjects affected / exposed                          | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| General disorders and administration site conditions |                   |                   |  |
| Adverse drug reaction                                |                   |                   |  |
| subjects affected / exposed                          | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Asthenia   |                   |                   |  |
| subjects affected / exposed                          | 3 / 2206 (0.14%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all      | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Chest pain   |                   |                   |  |
| subjects affected / exposed                          | 9 / 2206 (0.41%)  | 8 / 2343 (0.34%)  |  |
| occurrences causally related to treatment / all      | 0 / 9             | 0 / 9             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Death  |                   |                   |  |
| subjects affected / exposed                          | 16 / 2206 (0.73%) | 13 / 2343 (0.55%) |  |
| occurrences causally related to treatment / all      | 0 / 16            | 0 / 13            |  |
| deaths causally related to treatment / all           | 0 / 16            | 0 / 13            |  |
| Device dislocation                                   |                   |                   |  |
| subjects affected / exposed                          | 3 / 2206 (0.14%)  | 5 / 2343 (0.21%)  |  |
| occurrences causally related to treatment / all      | 0 / 5             | 0 / 5             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Chronic fatigue syndrome                             |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device failure                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foreign body reaction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Face oedema                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Gait disturbance                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammation                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated hernia                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hernia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malaise   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Medical device complication                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multi-organ failure                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3            |  |
| Nodule  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 7 / 2206 (0.32%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyp   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral swelling                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden death                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 1            |  |
| Sudden cardiac death                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ulcer haemorrhage                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Drug hypersensitivity                           |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Autoimmune disorder                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Anaphylactic reaction                           |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sarcoidosis                                     |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hypersensitivity                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Social circumstances                            |                   |                  |  |
| Physical assault                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Activities of daily living impaired             |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Reproductive system and breast disorders        |                   |                  |  |
| Cystocele                                       |                   |                  |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Breast mass                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colpocele                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial atrophy                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial metaplasia                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrocystic breast disease                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Female genital tract fistula                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mammary duct ectasia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metrorrhagia                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectocele                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine polyp                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 9 / 2206 (0.41%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal prolapse                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulval leukoplakia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute respiratory distress syndrome             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aspiration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Bronchial hyperreactivity                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Asthma  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atelectasis                                     |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchitis chronic                              |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchiectasis                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Dysphonia                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchomalacia                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                   |                  |  |
| subjects affected / exposed                     | 14 / 2206 (0.63%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Dyspnoea  |                   |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Dyspnoea exertional                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Epistaxis                                       |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoptysis                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Emphysema                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Interstitial lung disease                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung infiltration                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung disorder                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal cyst                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasal ulcer                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mediastinal cyst                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Painful respiration                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleurisy  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia aspiration                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary congestion                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 19 / 2206 (0.86%) | 13 / 2343 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 1 / 16            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 1             |  |
| Pneumothorax                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary mass                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary oedema                                |                   |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 5 / 2343 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1             |  |
| Pulmonary fibrosis                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory arrest                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory failure                             |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Tonsillar cyst                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tracheomalacia                                  |                   |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Psychiatric disorders                           |                   |                  |  |
| Anxiety   |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Aggression                                      |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Anxiety disorder                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Completed suicide                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Emotional distress                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Confusional state                               |                   |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Depression                                      |                   |                  |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hallucination                                   |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychotic disorder                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizophrenia, paranoid type                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Autoimmune hepatitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct obstruction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stenosis                              |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Biliary colic                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 5 / 2343 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholangitis                                     |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Biliary cirrhosis primary                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cholelithiasis                                  |                   |                   |  |
| subjects affected / exposed                     | 22 / 2206 (1.00%) | 30 / 2343 (1.28%) |  |
| occurrences causally related to treatment / all | 0 / 25            | 0 / 31            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cholecystitis acute                             |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cholecystitis                                   |                   |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gallbladder oedema                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gallbladder necrosis                            |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder polyp                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic failure                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Jaundice cholestatic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Blood pressure increased                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Antinuclear antibody positive                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carcinoembryonic antigen increased              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure orthostatic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Occult blood positive                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic enzyme increased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigation                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Troponin increased                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Protein total decreased                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight decreased                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Acetabulum fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone fissure                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain contusion                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Animal bite                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbon monoxide poisoning                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cartilage injury                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clavicle fracture                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cataract traumatic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%) | 8 / 2343 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Contusion                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dislocation of vertebra                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Craniocerebral injury                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Coronary artery restenosis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial bones fracture                           |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 9 / 2343 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 9             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Eye penetration                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femoral neck fracture                           |                   |                   |  |
| subjects affected / exposed                     | 16 / 2206 (0.73%) | 15 / 2343 (0.64%) |  |
| occurrences causally related to treatment / all | 1 / 16            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fall  |                   |                   |  |
| subjects affected / exposed                     | 13 / 2206 (0.59%) | 16 / 2343 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fibula fracture                                 |                   |                   |  |
| subjects affected / exposed                     | 14 / 2206 (0.63%) | 11 / 2343 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Foot fracture                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Femur fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 16 / 2206 (0.73%) | 12 / 2343 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fractured sacrum                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal stoma complication             |                   |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Graft complication                              |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hand fracture                                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Head injury                                     |                   |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Humerus fracture                                |                   |                  |  |
| subjects affected / exposed                     | 13 / 2206 (0.59%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hip fracture                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Injury corneal                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Incisional hernia                               |                   |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ilium fracture                                  |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament rupture                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament injury                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb crushing injury                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament sprain                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple injuries                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Perineal injury                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax traumatic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative hernia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative ileus                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Procedural hypotension                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Procedural pain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pubis fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation mucositis                             |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rib fracture                                    |                   |                   |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Road traffic accident                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| Radius fracture                                 |                   |                   |  |
| subjects affected / exposed                     | 25 / 2206 (1.13%) | 22 / 2343 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 26            | 0 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Scar  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Shunt malfunction                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skull fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skeletal injury                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin abrasion                                   |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Soft tissue injury                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Subdural haematoma                              |                   |                   |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Subdural haemorrhage                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tendon rupture                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thermal burn                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thoracic vertebral fracture                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 9 / 2343 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tibia fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 17 / 2206 (0.77%) | 12 / 2343 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transplant dysfunction                          |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ulna fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 9 / 2206 (0.41%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulnar nerve injury                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic intracranial haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound dehiscence                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Congenital ureteric anomaly                     |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cancer gene carrier                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Corneal dystrophy                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Muscular dystrophy                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac disorders                               |                   |                   |  |
| Acute myocardial infarction                     |                   |                   |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%)  | 18 / 2343 (0.77%) |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 4             |  |
| Acute coronary syndrome                         |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina unstable                                 |                   |                   |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%)  | 12 / 2343 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 7             | 1 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina pectoris                                 |                   |                   |  |
| subjects affected / exposed                     | 17 / 2206 (0.77%) | 19 / 2343 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 25            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Adams-Stokes syndrome                           |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Aortic valve incompetence                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Aortic valve disease                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Aortic valve stenosis                           |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arrhythmia supraventricular                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arrhythmia                                      |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arteriosclerosis coronary artery                |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial fibrillation                             |                   |                   |  |
| subjects affected / exposed                     | 50 / 2206 (2.27%) | 40 / 2343 (1.71%) |  |
| occurrences causally related to treatment / all | 4 / 69            | 0 / 47            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block                          |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial flutter                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block second degree            |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradycardia                                     |                   |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| Bundle branch block left                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac failure                                 |                   |                   |  |
| subjects affected / exposed                     | 15 / 2206 (0.68%) | 21 / 2343 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 24            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 5             |  |
| Cardiac failure acute                           |                   |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Cardiac disorder                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cardiac failure chronic                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cardiac failure congestive                      |                   |                  |  |
| subjects affected / exposed                     | 10 / 2206 (0.45%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1            |  |
| Cardiac fibrillation                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cardiac valve disease                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cardiac valve sclerosis                         |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cardiogenic shock                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Cardio-respiratory arrest                       |                   |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2             |  |
| Cardiomyopathy                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiopulmonary failure                         |                  |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1             |  |
| Chronic right ventricular failure               |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiovascular insufficiency                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Coronary artery occlusion                       |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Coronary artery disease                         |                  |                   |  |
| subjects affected / exposed                     | 9 / 2206 (0.41%) | 17 / 2343 (0.73%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Coronary artery insufficiency                   |                  |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Extrasystoles                                   |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive heart disease                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Heart valve calcification                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart valve incompetence                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left atrial dilatation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic cardiomyopathy                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular failure                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Mitral valve disease                            |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mitral valve disease mixed                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mitral valve incompetence                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myocardial infarction                           |                   |                   |  |
| subjects affected / exposed                     | 21 / 2206 (0.95%) | 24 / 2343 (1.02%) |  |
| occurrences causally related to treatment / all | 0 / 26            | 1 / 27            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 2             |  |
| Myocardial ischaemia                            |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 13 / 2343 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pericardial effusion                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Palpitations                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pericardial haemorrhage                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pericarditis                                    |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Right ventricular failure                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sinus arrest                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sinoatrial block                                |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sinus node dysfunction                          |                  |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 10 / 2343 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Supraventricular extrasystoles                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sinus bradycardia                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Supraventricular tachycardia                    |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Supraventricular tachyarrhythmia                |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachyarrhythmia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia induced cardiomyopathy              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tricuspid valve disease                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular arrhythmia                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular extrasystoles                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Acoustic neuritis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Akinesia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amnesia   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amyotrophic lateral sclerosis                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aphasia   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ataxia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery thrombosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carpal tunnel syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cauda equina syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar infarction                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral artery embolism                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral arteriosclerosis                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral atrophy                                |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebral haemorrhage                            |                   |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             |  |
| Cerebral infarction                             |                   |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%)  | 17 / 2343 (0.73%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 1 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cerebral thrombosis                             |                   |                   |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%)  | 8 / 2343 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebral ischaemia                              |                   |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 6 / 2343 (0.26%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebral microangiopathy                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebrovascular accident                        |                   |                   |  |
| subjects affected / exposed                     | 22 / 2206 (1.00%) | 29 / 2343 (1.24%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 30            |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 3             |  |
| Cerebrovascular disorder                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cerebrovascular insufficiency                   |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervicogenic headache                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cognitive disorder                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cubital tunnel syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic hyperosmolar coma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia Alzheimer's type                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Dysaesthesia                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic neuropathy                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Embolic stroke                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extrapyramidal disorder                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhage intracranial                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Facial paresis                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hemiparesis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic stroke                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoaesthesia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypotonia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive encephalopathy                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxic-ischaemic encephalopathy                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intercostal neuralgia                           |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intracranial aneurysm                           |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ischaemic cerebral infarction                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Loss of consciousness                           |                   |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ischaemic stroke                                |                   |                  |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Lacunar infarction                              |                   |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Lumbar radiculopathy                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Mental impairment                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Motor neurone disease                           |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Motor dysfunction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mononeuropathy multiplex                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myasthenia gravis                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorder                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic neuritis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraesthesia                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinson's disease                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinsonism                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial seizures                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudoradicular syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyneuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radicular syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiculitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyramidal tract syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiculopathy                                   |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sciatica  |                  |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 12 / 2343 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Seizure   |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Senile dementia                                 |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Spinal cord compression                         |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Subarachnoid haemorrhage                        |                  |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Sensory disturbance                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Tarsal tunnel syndrome                          |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Syncope   |                  |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 18 / 2206 (0.82%) | 20 / 2343 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thrombotic cerebral infarction                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transient global amnesia                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Trigeminal neuralgia                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| VIIth nerve paralysis                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transient ischaemic attack                      |                   |                   |  |
| subjects affected / exposed                     | 21 / 2206 (0.95%) | 19 / 2343 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vascular dementia                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vascular headache                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vertebrobasilar insufficiency                   |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Blood and lymphatic system disorders</b>     |                   |                   |  |
| <b>Anaemia</b>                                  |                   |                   |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 11 / 2343 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Haemorrhagic disorder</b>                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Bone marrow oedema</b>                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Leukopenia</b>                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Lymphadenitis</b>                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Iron deficiency anaemia</b>                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Lymphadenopathy</b>                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Microcytic anaemia</b>                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polycythaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenomegaly                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Deafness unilateral                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniere's disease                               |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hypoacusis                                      |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vertigo   |                   |                  |  |
| subjects affected / exposed                     | 14 / 2206 (0.63%) | 8 / 2343 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 1 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vertigo positional                              |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Otosclerosis                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vestibular disorder                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Eye disorders                                   |                   |                  |  |
| Blindness                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Blepharochalasis                                |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Blindness unilateral                            |                   |                  |  |

|  |                   |                   |  |
|--|-------------------|-------------------|--|
| subjects affected / exposed                      | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Cataract   |                   |                   |  |
| subjects affected / exposed                      | 17 / 2206 (0.77%) | 15 / 2343 (0.64%) |  |
| occurrences causally related to treatment / all  | 0 / 26            | 0 / 19            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Cataract diabetic                                |                   |                   |  |
| subjects affected / exposed                      | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Detachment of macular retinal pigment epithelium |                   |                   |  |
| subjects affected / exposed                      | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all  | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Diplopia   |                   |                   |  |
| subjects affected / exposed                      | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all  | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Eye haemorrhage                                  |                   |                   |  |
| subjects affected / exposed                      | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Ectropion  |                   |                   |  |
| subjects affected / exposed                      | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all  | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Glaucoma   |                   |                   |  |
| subjects affected / exposed                      | 3 / 2206 (0.14%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all  | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0             |  |
| Keratopathy                                      |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iridocyclitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular fibrosis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal detachment                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Maculopathy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Open angle glaucoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal tear                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal vascular thrombosis                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulcerative keratitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual impairment                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitreous haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal adhesions                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal distension                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal hernia obstructive                    |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Abdominal pain                                  |                   |                  |  |
| subjects affected / exposed                     | 10 / 2206 (0.45%) | 8 / 2343 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Abdominal rigidity                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Acquired oesophageal web                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Anal haemorrhage                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Anal prolapse                                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Anal sphincter atony                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Colitis   |                   |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Chronic gastritis                               |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coeliac disease                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis microscopic                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ulcerative                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Crohn's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diaphragmatic hernia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 9 / 2206 (0.41%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticular perforation                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum oesophageal                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer perforation                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysphagia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faecal incontinence                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epigastric discomfort                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis haemorrhagic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral hernia                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faeces discoloured                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 9 / 2343 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroduodenal ulcer                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis erosive                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal motility disorder              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal inflammation                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal mucosal disorder               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal stenosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematemesis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hiatus hernia                                   |                   |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ileus   |                   |                  |  |
| subjects affected / exposed                     | 7 / 2206 (0.32%)  | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hernial eventration                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Inguinal hernia                                 |                   |                  |  |
| subjects affected / exposed                     | 14 / 2206 (0.63%) | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal angina                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal fistula                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal haemorrhage                          |                   |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal ischaemia                            |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Intestinal obstruction                          |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0            |  |
| Intestinal perforation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal strangulation                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Irritable bowel syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine polyp                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestinal stenosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malabsorption                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mesenteric artery embolism                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Mechanical ileus                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Melaena   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal polyp                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic cyst                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic necrosis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis chronic                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis necrotising                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal perforation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngo-oesophageal diverticulum               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periodontal disease                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal polyp                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retroperitoneal haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal prolapse                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subileus  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stomatitis                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toothache                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tongue oedema                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Volvulus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Volvulus of small bowel                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Angioedema                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Decubitus ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis allergic                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug eruption                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lichenoid keratosis                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lichen sclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pemphigoid                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pruritus  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psoriasis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash pruritic                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin ulcer                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urticaria                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Bladder disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder irritation                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute kidney injury                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus bladder                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus ureteric                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus urethral                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic kidney disease                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Diabetic nephropathy                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis interstitial                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incontinence                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mixed incontinence                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrolithiasis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Nephropathy                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stress urinary incontinence                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tubulointerstitial nephritis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureteric stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral disorder                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary bladder polyp                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urge incontinence                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract obstruction                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Adrenal mass                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Goitre  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basedow's disease                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperthyroidism                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroiditis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inappropriate antidiuretic hormone secretion    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxic nodular goitre                            |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Arthralgia                                      |                   |                   |  |
| subjects affected / exposed                     | 10 / 2206 (0.45%) | 15 / 2343 (0.64%) |  |
| occurrences causally related to treatment / all | 1 / 10            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Acquired claw toe                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthritis                                       |                   |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 16 / 2206 (0.73%) | 10 / 2343 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthropathy                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bone loss                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bone disorder                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bone pain                                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chondrocalcinosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bursitis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Compartment syndrome                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dupuytren's contracture                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chondropathy                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fistula   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibromyalgia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture pain                                   |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Haemarthrosis                                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Foot deformity                                  |                   |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intervertebral disc disorder                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intervertebral disc degeneration                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intervertebral disc protrusion                  |                   |                  |  |
| subjects affected / exposed                     | 12 / 2206 (0.54%) | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Joint effusion                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Joint swelling                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Lumbar spinal stenosis                          |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kyphosis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mobility decreased                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Monarthrititis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Morphoea  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal chest pain                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal pain                            |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 1 / 4             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myopathy  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Nodal osteoarthritis                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Neck pain                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoarthropathy                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteochondrosis                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoarthritis                                  |                   |                   |  |
| subjects affected / exposed                     | 79 / 2206 (3.58%) | 99 / 2343 (4.23%) |  |
| occurrences causally related to treatment / all | 1 / 87            | 0 / 118           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteonecrosis of jaw                            |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 6 / 2343 (0.26%)  |  |
| occurrences causally related to treatment / all | 3 / 3             | 7 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteonecrosis                                   |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain in extremity                               |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteoporosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain in jaw                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periarthritis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plica syndrome                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polymyalgia rheumatica                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudarthrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhabdomyolysis                                  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rotator cuff syndrome                           |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rheumatoid arthritis                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sacroiliitis                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Seronegative arthritis                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sjogren's syndrome                              |                   |                   |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Spinal column stenosis                          |                   |                   |  |
| subjects affected / exposed                     | 14 / 2206 (0.63%) | 22 / 2343 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 1 / 27            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Spinal osteoarthritis                           |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Spinal pain                                     |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondyloarthropathy                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial cyst                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylolisthesis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial disorder                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic lupus erythematosus                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendonitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal sepsis                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendiceal abscess                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess neck                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis bacterial                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atypical pneumonia                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis infective                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacteraemia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial pyelonephritis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchopneumonia                                |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Bronchitis                                      |                  |                  |  |
| subjects affected / exposed                     | 8 / 2206 (0.36%) | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchitis fungal                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulitis                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis infective                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile infection                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic tonsillitis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic sinusitis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dengue fever                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 5 / 2343 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device related infection                        |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Ear infection                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diverticulitis                                  |                   |                   |  |
| subjects affected / exposed                     | 11 / 2206 (0.50%) | 10 / 2343 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Endocarditis                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Enterocolitis bacterial                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Erysipelas                                      |                   |                   |  |
| subjects affected / exposed                     | 4 / 2206 (0.18%)  | 9 / 2343 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 9             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis                                 |                   |                   |  |
| subjects affected / exposed                     | 9 / 2206 (0.41%)  | 9 / 2343 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gangrene  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis viral                           |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal infection                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Helicobacter gastritis                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemophilus infection                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| H1N1 influenza                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis C                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cyst infection                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                                   | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 1            | 0 / 0            |  |
| Infection   |                  |                  |  |
| subjects affected / exposed                                   | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Influenza   |                  |                  |  |
| subjects affected / exposed                                   | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Infective exacerbation of chronic obstructive airways disease |                  |                  |  |
| subjects affected / exposed                                   | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Klebsiella infection  |                  |                  |  |
| subjects affected / exposed                                   | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Klebsiella bacteraemia  |                  |                  |  |
| subjects affected / exposed                                   | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Liver abscess   |                  |                  |  |
| subjects affected / exposed                                   | 0 / 2206 (0.00%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Listeriosis   |                  |                  |  |
| subjects affected / exposed                                   | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Laryngitis  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lobar pneumonia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 4 / 2343 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 6 / 2343 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lymph node tuberculosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung infection                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis viral                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis aseptic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mycobacterium avium complex infection           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenic sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrotising fasciitis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Onychomycosis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis media                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parotitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia                                       |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 44 / 2206 (1.99%) | 48 / 2343 (2.05%) |  |
| occurrences causally related to treatment / all | 0 / 52            | 0 / 59            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 2             |  |
| Pneumonia bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 4 / 2343 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia influenzal                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia pneumococcal                          |                   |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia haemophilus                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia pseudomonal                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia staphylococcal                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia streptococcal                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Post procedural infection                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomembranous colitis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary tuberculosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salmonellosis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis chronic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory tract infection                     |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Salpingo-oophoritis                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Salpingitis                                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Septic shock                                    |                  |                   |  |
| subjects affected / exposed                     | 5 / 2206 (0.23%) | 5 / 2343 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3             |  |
| Sepsis  |                  |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 15 / 2343 (0.64%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2             |  |
| Skin infection                                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sinusitis                                       |                  |                   |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Small intestine gangrene                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Soft tissue infection                           |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal bacteraemia                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Stenotrophomonas infection                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tick-borne viral encephalitis                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous abscess                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural empyema                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth infection                                 |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tuberculosis                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tracheobronchitis                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tracheitis                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%)  | 0 / 2343 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 2 / 2343 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tuberculosis of peripheral lymph nodes          |                   |                   |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%)  | 1 / 2343 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 13 / 2206 (0.59%) | 11 / 2343 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urosepsis                                       |                   |                   |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%)  | 3 / 2343 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vaginal infection                               |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular neuronitis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral infection                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound infection                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2206 (0.14%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Cachexia  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 6 / 2206 (0.27%) | 7 / 2343 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Diabetes mellitus                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus inadequate control            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Failure to thrive                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercalcaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 3 / 2343 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Electrolyte imbalance                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercholesterolaemia                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypocalcaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkalaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2206 (0.05%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2206 (0.18%) | 2 / 2343 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Hypokalaemia</b>                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Metabolic acidosis</b>                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 0 / 2343 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Type 2 diabetes mellitus</b>                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2206 (0.09%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vitamin B12 deficiency</b>                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2206 (0.00%) | 1 / 2343 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                            | Placebo/Denosumab<br>60 mg Q6M | Denosumab/Denosu<br>mab 60 mg Q6M |  |
|--|--------------------------------|-----------------------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                                |                                   |  |
| subjects affected / exposed                                  | 1809 / 2206<br>(82.00%)        | 1920 / 2343<br>(81.95%)           |  |
| <b>Injury, poisoning and procedural complications</b>        |                                |                                   |  |
| <b>Fall</b>  |                                |                                   |  |
| subjects affected / exposed                                  | 240 / 2206<br>(10.88%)         | 268 / 2343<br>(11.44%)            |  |
| occurrences (all)  | 338                            | 373                               |  |
| <b>Contusion</b>   |                                |                                   |  |
| subjects affected / exposed                                  | 181 / 2206 (8.20%)             | 176 / 2343 (7.51%)                |  |
| occurrences (all)  | 251                            | 245                               |  |
| <b>Vascular disorders</b>                                    |                                |                                   |  |

|   |   |   |  |
|---|---|---|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 460 / 2206<br>(20.85%)<br>581   | 498 / 2343<br>(21.25%)<br>606   |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Sciatica<br>subjects affected / exposed<br>occurrences (all) | <br>173 / 2206 (7.84%)<br>203<br><br>121 / 2206 (5.49%)<br>158<br><br>149 / 2206 (6.75%)<br>175 | <br>163 / 2343 (6.96%)<br>193<br><br>103 / 2343 (4.40%)<br>120<br><br>165 / 2343 (7.04%)<br>198 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | <br>141 / 2206 (6.39%)<br>169   | <br>168 / 2343 (7.17%)<br>194   |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)  | <br>138 / 2206 (6.26%)<br>174   | <br>140 / 2343 (5.98%)<br>177   |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)   | <br>319 / 2206<br>(14.46%)<br>492   | <br>317 / 2343<br>(13.53%)<br>467   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)   | <br>139 / 2206 (6.30%)<br>169<br><br>141 / 2206 (6.39%)<br>147                                  | <br>152 / 2343 (6.49%)<br>175<br><br>118 / 2343 (5.04%)<br>134                                  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | <br>172 / 2206 (7.80%)<br>217   | <br>168 / 2343 (7.17%)<br>204   |  |
| Psychiatric disorders   |   |   |  |

|   |                            |                            |  |
|---|----------------------------|----------------------------|--|
| Depression<br>subjects affected / exposed<br>occurrences (all)              | 135 / 2206 (6.12%)<br>161  | 143 / 2343 (6.10%)<br>161  |  |
| Musculoskeletal and connective tissue disorders                             |                            |                            |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)              | 527 / 2206 (23.89%)<br>755 | 541 / 2343 (23.09%)<br>763 |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)          | 332 / 2206 (15.05%)<br>449 | 355 / 2343 (15.15%)<br>484 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)               | 501 / 2206 (22.71%)<br>693 | 493 / 2343 (21.04%)<br>665 |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)    | 197 / 2206 (8.93%)<br>243  | 231 / 2343 (9.86%)<br>290  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)       | 264 / 2206 (11.97%)<br>333 | 293 / 2343 (12.51%)<br>387 |  |
| Infections and infestations   |                            |                            |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 372 / 2206 (16.86%)<br>565 | 385 / 2343 (16.43%)<br>576 |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)               | 179 / 2206 (8.11%)<br>225  | 192 / 2343 (8.19%)<br>238  |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                | 194 / 2206 (8.79%)<br>372  | 212 / 2343 (9.05%)<br>396  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)              | 206 / 2206 (9.34%)<br>290  | 226 / 2343 (9.65%)<br>350  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 242 / 2206 (10.97%)<br>385 | 250 / 2343 (10.67%)<br>389 |  |

|                                    |                    |                    |  |
|------------------------------------|--------------------|--------------------|--|
| Pneumonia                          |                    |                    |  |
| subjects affected / exposed        | 137 / 2206 (6.21%) | 167 / 2343 (7.13%) |  |
| occurrences (all)                  | 217                | 246                |  |
| Upper respiratory tract infection  |                    |                    |  |
| subjects affected / exposed        | 139 / 2206 (6.30%) | 128 / 2343 (5.46%) |  |
| occurrences (all)                  | 169                | 159                |  |
| Metabolism and nutrition disorders |                    |                    |  |
| Hypercholesterolaemia              |                    |                    |  |
| subjects affected / exposed        | 215 / 2206 (9.75%) | 200 / 2343 (8.54%) |  |
| occurrences (all)                  | 223                | 207                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 25 October 2007   | <ul style="list-style-type: none"><li>- Added a PK/PD substudy to provide additional data to characterize the PK and PD profiles at additional time points during the subject's dosing interval.</li><li>- Incorporated investigational product from a new manufacturing facility (BIP) to be administered by prefilled syringe.</li><li>- Added an assessment of antidenosumab antibodies at extension month 6 in subjects who received investigational product from BIP to evaluate the immunogenicity for BIP drug substance in prefilled syringes.</li></ul> |
| 09 March 2009     | <ul style="list-style-type: none"><li>- Extended the study beyond extension month 24 for 5 additional years to allow reporting of descriptive analyses of safety and assessments of the cumulative effect of denosumab on BMD, BTMs, and vertebral and nonvertebral fractures following up to ten years of therapy.</li></ul>  |
| 01 September 2010 | <ul style="list-style-type: none"><li>- Added procedures to assess incident vertebral fractures at 2-year intervals starting at year 3.</li></ul>  |
| 13 January 2013   | <ul style="list-style-type: none"><li>- Updated the procedures for reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities.</li></ul>   |
| 15 May 2014       | <ul style="list-style-type: none"><li>- Added quantitative computer tomography assessments for a subset of approximately 30 subjects who had participated in a similar substudy in Study 20030216.</li><li>- Added blood sample collection to analyze bone turnover markers CTX-1 and P1NP.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported