



## Clinical trial results:

### A Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study of Denosumab as Adjuvant Treatment for Women With Early-stage Breast Cancer at High Risk of Recurrence (D-CARE)

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2009-011299-32                                     |
| Trial protocol           | PT HU GB ES CZ LV FR BE SK NL IE DK SI GR IT BG DE |
| Global end of trial date | 26 March 2018                                      |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 10 April 2019 |
| First version publication date | 10 April 2019 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20060359 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01077154 |
| 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, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, 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                       | 26 March 2018 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 March 2018 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the treatment effect of denosumab with that of placebo on prolonging bone metastasis-free survival in subjects with early-stage breast cancer at high risk of disease recurrence.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable federal and local regulations/guidelines.

The protocol, proposed informed consent form (ICF), other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval before recruitment of subjects in the study and the shipment of investigational product.

The investigator was responsible for obtaining written informed consent after the aims, methods, and potential hazards of the study were adequately explained.

Informed consent was obtained before any protocol-specific screening procedures and before any investigational product was administered.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 02 June 2010     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 5 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Spain: 373          |
| Country: Number of subjects enrolled | Australia: 297      |
| Country: Number of subjects enrolled | United Kingdom: 237 |
| Country: Number of subjects enrolled | Belgium: 228        |
| Country: Number of subjects enrolled | France: 170         |
| Country: Number of subjects enrolled | Greece: 103         |
| Country: Number of subjects enrolled | Ireland: 75         |
| Country: Number of subjects enrolled | Netherlands: 67     |
| Country: Number of subjects enrolled | Denmark: 55         |
| Country: Number of subjects enrolled | Portugal: 51        |
| Country: Number of subjects enrolled | Italy: 46           |
| Country: Number of subjects enrolled | Germany: 41         |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Israel: 17              |
| Country: Number of subjects enrolled | United States: 715      |
| Country: Number of subjects enrolled | Canada: 287             |
| Country: Number of subjects enrolled | Hungary: 232            |
| Country: Number of subjects enrolled | Czech Republic: 121     |
| Country: Number of subjects enrolled | Russian Federation: 118 |
| Country: Number of subjects enrolled | Poland: 92              |
| Country: Number of subjects enrolled | Latvia: 35              |
| Country: Number of subjects enrolled | Bulgaria: 35            |
| Country: Number of subjects enrolled | Slovakia: 29            |
| Country: Number of subjects enrolled | Romania: 17             |
| Country: Number of subjects enrolled | Slovenia: 9             |
| Country: Number of subjects enrolled | Serbia: 4               |
| Country: Number of subjects enrolled | Japan: 262              |
| Country: Number of subjects enrolled | India: 174              |
| Country: Number of subjects enrolled | Korea, Republic of: 78  |
| Country: Number of subjects enrolled | Taiwan: 43              |
| Country: Number of subjects enrolled | Philippines: 32         |
| Country: Number of subjects enrolled | Hong Kong: 32           |
| Country: Number of subjects enrolled | Malaysia: 15            |
| Country: Number of subjects enrolled | Brazil: 200             |
| Country: Number of subjects enrolled | South Africa: 63        |
| Country: Number of subjects enrolled | Mexico: 53              |
| Country: Number of subjects enrolled | Chile: 34               |
| Country: Number of subjects enrolled | Peru: 28                |
| Country: Number of subjects enrolled | Argentina: 22           |
| Country: Number of subjects enrolled | Turkey: 19              |
| Worldwide total number of subjects   | 4509                    |
| EEA total number of subjects         | 2016                    |

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)                      | 3919 |
| From 65 to 84 years                       | 588  |
| 85 years and over                         | 2    |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 407 centers in Australia, Western Europe, Eastern Europe, Israel, North America, Asia, South America, South Africa, and Turkey from 02 June 2010 to 24 August 2012.

### Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to 1 of 2 groups. Randomization was stratified based on breast cancer therapy/lymph node (LN) status, hormone receptor status, human epidermal growth factor receptor 2 (HER-2) status, age, and geographic region.

### Period 1

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

### Arms

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

Arm description:

Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Administered subcutaneously for up to 5 years.

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

Arm description:

Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Denosumab              |
| Investigational medicinal product code | AMG 162                |
| Other name                             | XGEVA®                 |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Administered subcutaneously for up to 5 years.

| <b>Number of subjects in period 1</b>     | Placebo | Denosumab |
|---|---------|-----------|
| Started                                   | 2253    | 2256      |
| Received Study Drug                       | 2229    | 2230      |
| Completed                                 | 27      | 28        |
| Not completed                             | 2226    | 2228      |
| Consent withdrawn by subject              | 369     | 385       |
| Ineligibility Determined                  | 10      | 14        |
| Protocol-specified Criteria (Study Ended) | 1524    | 1514      |
| Adverse event, non-fatal                  | 9       | 9         |
| Protocol Deviation                        | 1       | -         |
| Death                                     | 215     | 214       |
| Other                                     | 14      | 11        |
| Administrative Decision                   | 1       | 6         |
| Lost to follow-up                         | 43      | 35        |
| Disease Progression                       | 18      | 20        |
| Noncompliance                             | 22      | 20        |

## Baseline characteristics

### Reporting groups

|   |           |
|---|-----------|
| Reporting group title   | Placebo   |
| Reporting group description:  |           |
| Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.                   |           |
| Reporting group title   | Denosumab |
| Reporting group description:  |           |
| Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years. |           |

| Reporting group values  | Placebo | Denosumab | Total |
|---|---------|-----------|-------|
| Number of subjects  | 2253    | 2256      | 4509  |
| Age, Customized   |         |           |       |
| Units: Subjects   |         |           |       |
| 18 - 64 years   | 1960    | 1959      | 3919  |
| 65 - 74 years   | 259     | 260       | 519   |
| 75 - 84 years   | 33      | 36        | 69    |
| ≥ 85 years  | 1       | 1         | 2     |
| Age Continuous  |         |           |       |
| Units: years  |         |           |       |
| arithmetic mean   | 51.6    | 51.4      | -     |
| standard deviation  | ± 10.6  | ± 10.7    | -     |
| Sex: Female, Male   |         |           |       |
| Units: Subjects   |         |           |       |
| Female  | 2253    | 2256      | 4509  |
| Male  | 0       | 0         | 0     |
| Race/Ethnicity, Customized  |         |           |       |
| Units: Subjects   |         |           |       |
| White   | 1692    | 1676      | 3368  |
| Asian   | 222     | 213       | 435   |
| Japanese  | 134     | 135       | 269   |
| Hispanic/Latino   | 112     | 135       | 247   |
| Black   | 70      | 74        | 144   |
| Native Hawaiian or Other Pacific Islander   | 4       | 3         | 7     |
| American Indian or Alaska Native  | 1       | 0         | 1     |
| Other   | 18      | 20        | 38    |
| Menopausal Status   |         |           |       |
| Units: Subjects   |         |           |       |
| Premenopausal   | 1165    | 1195      | 2360  |
| Postmenopausal  | 1088    | 1061      | 2149  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status  |         |           |       |
| A scale to assess a patient's disease status.<br>0 = Fully active, able to carry out all pre-disease performance without restriction;<br>1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature;<br>2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about > 50% of waking hours; |         |           |       |

3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours;  
4 = Completely disabled, confined to bed or chair;  
5 = Dead.

|                                |      |      |      |
|--------------------------------|------|------|------|
| Units: Subjects                |      |      |      |
| 0 (Fully active)               | 1913 | 1922 | 3835 |
| 1 (Restricted but ambulatory)  | 340  | 329  | 669  |
| 2 (Ambulatory, unable to work) | 0    | 3    | 3    |
| Missing                        | 0    | 2    | 2    |

|  |  |  |  |
|--|--|--|--|
| Breast Cancer Therapy / Lymph Node Status (Strata per Randomization) |  |  |  |
|--|--|--|--|

Breast cancer therapy / lymph node (LN) status:  
a. neo-adjuvant therapy / any LN status;  
b. adjuvant therapy / LN negative (based on axillary LN dissection, or based on sentinel node [SN] status);  
c. adjuvant therapy / LN positive

|  |      |      |      |
|--|------|------|------|
| Units: Subjects                              |      |      |      |
| Neo-adjuvant therapy / any lymph node status | 550  | 552  | 1102 |
| Adjuvant therapy / lymph node negative       | 68   | 65   | 133  |
| Adjuvant therapy / lymph node positive       | 1635 | 1639 | 3274 |

|  |  |  |  |
|--|--|--|--|
| Hormone Receptor Status (Strata per Randomization) |  |  |  |
|--|--|--|--|

Hormone receptor (estrogen receptor [ER] / progesterone receptor [PR]) status  
a. ER and/or PR positive  
b. ER and PR negative

|                       |      |      |      |
|-----------------------|------|------|------|
| Units: Subjects       |      |      |      |
| ER and/or PR positive | 1740 | 1747 | 3487 |
| ER and PR negative    | 513  | 509  | 1022 |

|  |  |  |  |
|--|--|--|--|
| Human Epidermal Growth Factor Receptor 2 (HER-2) Status (Strata per Randomization) |  |  |  |
|--|--|--|--|

|                 |      |      |      |
|-----------------|------|------|------|
| Units: Subjects |      |      |      |
| HER-2 positive  | 490  | 492  | 982  |
| HER-2 negative  | 1763 | 1764 | 3527 |

|                                |  |  |  |
|--------------------------------|--|--|--|
| Age (Strata per Randomization) |  |  |  |
|--------------------------------|--|--|--|

|                 |      |      |      |
|-----------------|------|------|------|
| Units: Subjects |      |      |      |
| < 50 years      | 1026 | 1029 | 2055 |
| ≥ 50 years      | 1227 | 1227 | 2454 |

|  |  |  |  |
|--|--|--|--|
| Geographic Region (Strata per Randomization) |  |  |  |
|--|--|--|--|

|                 |      |      |      |
|-----------------|------|------|------|
| Units: Subjects |      |      |      |
| Japan           | 131  | 131  | 262  |
| Other           | 2122 | 2125 | 4247 |

|                                     |  |  |  |
|-------------------------------------|--|--|--|
| Molecular Subtypes of Breast Cancer |  |  |  |
|-------------------------------------|--|--|--|

Hormone receptor (HR; estrogen receptor [ER] / progesterone receptor [PR]); HR positive = ER and/or PR positive; HR negative = ER and PR negative

|                                |      |      |      |
|--------------------------------|------|------|------|
| Units: Subjects                |      |      |      |
| HR positive and HER-2 positive | 288  | 286  | 574  |
| HR positive and HER-2 negative | 1460 | 1458 | 2918 |
| HR negative and HER-2 positive | 163  | 168  | 331  |
| HR negative and HER-2 negative | 341  | 343  | 684  |
| Missing                        | 1    | 1    | 2    |

|                   |  |  |  |
|-------------------|--|--|--|
| Lymph Node Status |  |  |  |
|-------------------|--|--|--|

Clinical and pathologic regional lymph node (LN) status (by American Joint Committee on Cancer (AJCC)):

N0 = no LN metastasis or pathologic (p) micrometastases <2.0 mm;  
N1 = Ipsilateral level I, II axillary (Ax) LN or p micrometastases >2.0mm or in internal mammary (IM) LN;  
N2 = fixed ipsilateral level I, II Ax LNs or clinically detected IM LNs only or pLN metastases in 4-9 Ax LNs;  
N3 = ipsilateral level III infraclavicular (IC) LNs or clinically detected IM LNs with other level I/II Ax LNs or supraclavicular (SC) LNs or pLN metastases in ≥10 Ax LNs;  
NX = LNs cannot be assessed.

| Units: Subjects |      |      |      |
|-----------------|------|------|------|
| N0              | 130  | 131  | 261  |
| N1              | 1369 | 1381 | 2750 |
| N2              | 506  | 505  | 1011 |
| N3              | 230  | 224  | 454  |
| Nx              | 18   | 15   | 33   |

| Breast Cancer Histopathologic Grade |  |  |  |
|-------------------------------------|--|--|--|
|-------------------------------------|--|--|--|

Tumor grade was determined according to the Nottingham Combined Histological Grading System, based on morphological features (tubule formation, nuclear pleomorphism, and mitotic count), by assigning a value of 1 (favorable) to 3 (unfavorable) for each feature. Scores for the 3 categories were added to give a combined histopathologic grade score:

Grade (G)1 (low grade; favorable) = total score of 3, 4, or 5;

G2 (intermediate) = total score of 6 or 7;

G3 (high; unfavorable) = total score of 8 or 9.

| Units: Subjects        |      |      |      |
|------------------------|------|------|------|
| Grade 1 = Low          | 222  | 209  | 431  |
| Grade 2 = Intermediate | 1015 | 1079 | 2094 |
| Grade 3 = High         | 938  | 906  | 1844 |
| Not Evaluable/Missing  | 78   | 62   | 140  |



## End points

### End points reporting groups

|   |           |
|---|-----------|
| Reporting group title   | Placebo   |
| Reporting group description:  |           |
| Participants were randomized to receive placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.                   |           |
| Reporting group title   | Denosumab |
| Reporting group description:  |           |
| Participants were randomized to receive denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years. |           |

### Primary: Bone Metastasis-free Survival (BMFS)

|   |                                      |
|---|--------------------------------------|
| End point title   | Bone Metastasis-free Survival (BMFS) |
| End point description:  |                                      |
| BMFS time was defined as the time interval from the randomization date to the first occurrence of bone metastasis or death from any cause, whichever came first. Participants last known to be alive with no bone metastasis were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first occurrence of bone metastasis before randomization were censored at their randomization date. Bone metastasis must have been confirmed by central imaging analysis or by biopsy. Evidence of disseminated tumor cells in bone marrow was not sufficient for determination of disease recurrence. Development of new primary malignancy in bone was not considered as bone metastasis. Since the median BMFS time could not be estimated due to low number of events, the percentage of participants with an event (i.e., bone metastasis or death) is reported. |                                      |
| End point type  | Primary                              |
| End point timeframe:  |                                      |
| From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.   |                                      |

| End point values                  | Placebo             | Denosumab           |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 2253                | 2256                |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 13.5 (12.1 to 15.0) | 12.9 (11.6 to 14.3) |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Analysis of Bone Metastasis-free Survival |
| Statistical analysis description:   |   |
| The hazard ratio of denosumab compared with placebo and its corresponding 2-sided 95% confidence interval was estimated using a Cox proportional hazards model with treatment groups as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab. |   |
| Comparison groups   | Placebo v Denosumab                       |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 4509                 |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | = 0.7 <sup>[1]</sup> |
| Method                                  | Stratified Log Rank  |
| Parameter estimate                      | Hazard ratio (HR)    |
| Point estimate                          | 0.97                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.82                 |
| upper limit                             | 1.14                 |

Notes:

[1] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

## Secondary: Disease-free Survival (DFS)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Disease-free Survival (DFS) |
|-----------------|-----------------------------|

End point description:

DFS time was defined as the time interval from the randomization date to the date of first observation of disease recurrence or death from any cause, whichever was first. Participants last known to be alive with no disease recurrence were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first disease recurrence before randomization were censored at their randomization date. Disease recurrence includes bone metastasis and extraosseous disease (EOD) confirmed by central imaging analysis or by biopsy/cytology. Development of non-breast cancer new primary malignancy was not considered as disease recurrence. Since the median DFS time could not be estimated due to low number of events, the percentage of participants with an event (i.e., disease recurrence or death) is reported.

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

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

| End point values                  | Placebo             | Denosumab           |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 2253                | 2256                |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 19.2 (17.6 to 20.8) | 19.6 (18.0 to 21.2) |  |  |

## Statistical analyses

|                            |                                   |
|----------------------------|-----------------------------------|
| Statistical analysis title | Analysis of Disease-free Survival |
|----------------------------|-----------------------------------|

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors; a hazard ratio < 1 favors denosumab.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Placebo v Denosumab |
|-------------------|---------------------|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 4509                  |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.57 <sup>[2]</sup> |
| Method                                  | Stratified Log Rank   |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.04                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.91                  |
| upper limit                             | 1.19                  |

Notes:

[2] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

## Secondary: Disease-free Survival (DFS) in the Postmenopausal Subset

|                 |  |
|-----------------|--|
| End point title | Disease-free Survival (DFS) in the Postmenopausal Subset |
|-----------------|--|

End point description:

DFS time was defined as the time interval from the randomization date to the date of first observation of disease recurrence or death from any cause, whichever was first. Participants last known to be alive with no disease recurrence were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first disease recurrence before randomization were censored at their randomization date. Disease recurrence includes bone metastasis and extraosseous disease (EOD) confirmed by central imaging analysis or by biopsy/cytology. Development of non-breast cancer new primary malignancy was not considered as disease recurrence. Since the median DFS time in the postmenopausal subset could not be estimated due to low number of events, the percentage of participants with an event (i.e., disease recurrence or death) is reported.

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

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

| End point values                  | Placebo             | Denosumab           |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 1088                | 1061                |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 18.6 (16.3 to 20.9) | 20.3 (17.8 to 22.7) |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of DFS in Postmenopausal Subset |
|----------------------------|--|

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors; a hazard ratio < 1 favors denosumab.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Placebo v Denosumab |
|-------------------|---------------------|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 2149                  |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.26 <sup>[3]</sup> |
| Method                                  | Stratified Log Rank   |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.12                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.92                  |
| upper limit                             | 1.36                  |

Notes:

[3] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

## Secondary: Overall Survival

|   |                  |
|---|------------------|
| End point title   | Overall Survival |
| End point description:  |                  |
| Overall survival (OS) time was defined as the time interval from the randomization date to the date of death from any cause. Participants last known to be alive were censored at their last contact date. Since the median time to overall survival could not be estimated at the time of the final analysis due to low numbers of events, the percentage of participants with an event (i.e., death) is reported. |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| From randomization until the end of study; median (minimum, maximum) time on study was 72.7 (0, 92) and 72.3 (0, 92) months in each treatment group respectively.   |                  |

| End point values                  | Placebo           | Denosumab         |  |  |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed       | 2253              | 2256              |  |  |
| Units: percentage of participants |                   |                   |  |  |
| number (confidence interval 95%)  | 9.5 (8.3 to 10.8) | 9.5 (8.3 to 10.7) |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title  | Analysis of Overall Survival |
| Statistical analysis description:   |                              |
| The hazard ratio and its 2-sided 95% CI were estimated using a Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab. |                              |
| Comparison groups   | Placebo v Denosumab          |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 4509                  |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.94 <sup>[4]</sup> |
| Method                                  | Stratified Log Rank   |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.01                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.83                  |
| upper limit                             | 1.22                  |

Notes:

[4] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

## Secondary: Distant Recurrence-free Survival

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Distant Recurrence-free Survival |
|-----------------|----------------------------------|

End point description:

Distant recurrence-free survival (DRFS) was defined as the time interval from the randomization date to the date of first observation of distant disease recurrence or death from any cause, whichever came first. Participants last known to be alive, who had not experienced distant disease recurrence, were censored at their last assessment date, or at the primary analysis data cut-off date, whichever was first. Participants who had first distant recurrence before randomization were censored at their randomization date. Distant disease recurrence includes confirmed bone metastasis and extraosseous disease other than local-regional disease recurrence. Development of non-breast cancer new primary malignancy was not considered as distant disease recurrence. Since the median time to DRFS could not be estimated due to the low number of events, the percentage of participants with an event (i.e., distant recurrence or death) is reported.

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

End point timeframe:

From randomization until the primary analysis data cut-off date of 31 August 2017; median (minimum, maximum) time on study was 67.2 (0.0, 85.9) and 67.0 (0.0, 86.6) months in each treatment group respectively.

| End point values                  | Placebo             | Denosumab           |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 2253                | 2256                |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 18.0 (16.4 to 19.6) | 18.7 (17.1 to 20.3) |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of Distant Recurrence-free Survival |
|----------------------------|--|

Statistical analysis description:

The hazard ratio and its 2-sided 95% CI were estimated using Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Placebo v Denosumab |
|-------------------|---------------------|

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 4509                  |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.41 <sup>[5]</sup> |
| Method                                  | Stratified Log Rank   |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.06                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.92                  |
| upper limit                             | 1.21                  |

Notes:

[5] - Log rank test stratified by breast cancer therapy/LN status, hormone receptor status, HER-2 status, age, and geographic region.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose; median time on treatment was 59 months in each arm. Total deaths includes deaths from first dose of study drug to the end of study date; median time on study was 72.5 months overall.

Adverse event reporting additional description:

Data are reported for all randomized subjects who received  $\geq 1$  dose of investigational product. Subjects were analyzed according to their actual treatment received; eleven participants randomized to the placebo group received at least 1 dose of denosumab during the study and are counted in the denosumab group for safety analyses.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

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

Reporting group description:

Participants received placebo subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by placebo subcutaneous injections once every 3 months for 4.5 years.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Denosumab |
|-----------------------|-----------|

Reporting group description:

Participants received denosumab 120 mg subcutaneous injections once every 3 or 4 weeks for approximately 6 months followed by denosumab 120 mg subcutaneous injections once every 3 months for 4.5 years.

| Serious adverse events  | Placebo                | Denosumab              |  |
|---|------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                        |                        |  |
| subjects affected / exposed   | 675 / 2218<br>(30.43%) | 702 / 2241<br>(31.33%) |  |
| number of deaths (all causes)                                       | 215                    | 215                    |  |
| number of deaths resulting from adverse events                      |                        |                        |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |  |
| Acrochordon   |                        |                        |  |
| subjects affected / exposed   | 1 / 2218 (0.05%)       | 0 / 2241 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Acute leukaemia   |                        |                        |  |
| subjects affected / exposed   | 0 / 2218 (0.00%)       | 1 / 2241 (0.04%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                  | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Acute myeloid leukaemia   |                        |                        |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Adenocarcinoma                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Adenocarcinoma gastric                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenocarcinoma of colon                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenolipoma                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendix cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell lymphoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell small lymphocytic lymphoma               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 0 / 2218 (0.00%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign neoplasm of thymus                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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 thyroid gland                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma stage III   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone neoplasm                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bowen's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain cancer metastatic                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cancer                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 8 / 2241 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |  |
| Breast cancer metastatic                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Breast cancer recurrent                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cancer pain                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chest wall tumour                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic myeloid leukaemia                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 2218 (0.23%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Colorectal adenocarcinoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial adenocarcinoma                      |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Endometrial adenoma                                  |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (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                          | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Endometrial cancer stage I                           |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Endometrial stromal sarcoma                          |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Extranodal marginal zone B-cell lymphoma (MALT type) |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Fallopian tube cancer                                |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Gastric cancer                                       |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 0            |  |
| Gastric neoplasm                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal metastasis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intraductal proliferative breast lesion         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive ductal breast carcinoma                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine benign neoplasm                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leiomyoma                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leiomyosarcoma metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 3 / 2218 (0.14%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Lung adenocarcinoma stage IV                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lung cancer metastatic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung neoplasm malignant                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphangiosis carcinomatosa                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma stage III                    |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant neoplasm of thorax                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Malignant neoplasm progression                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant pleural effusion                      |                   |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Meningioma                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Metastases to bone                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Metastases to breast                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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                     | 17 / 2218 (0.77%) | 15 / 2241 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 4             |  |
| Metastases to liver                             |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastases to lymph nodes                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to meninges                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Metastases to ovary                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to peritoneum                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastases to skin                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic neoplasm                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-small cell lung cancer stage I              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal neoplasm                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer stage III                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ovarian epithelial cancer                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian neoplasm                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paget's disease of the vulva                    |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papillary thyroid cancer                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraneoplastic syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Parathyroid tumour benign                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenocarcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cancer stage I                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cell carcinoma                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retro-orbital neoplasm                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestine carcinoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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 the cervix           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thymoma   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid neoplasm                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine leiomyoma                               |                  |                  |  |
| subjects affected / exposed                     | 5 / 2218 (0.23%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Astrocytoma                                     |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Papilloma                                       |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vascular disorders                              |                   |                  |  |
| Aortic stenosis                                 |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Arteritis                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Brachiocephalic vein thrombosis                 |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Circulatory collapse                            |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Deep vein thrombosis                            |                   |                  |  |
| subjects affected / exposed                     | 12 / 2218 (0.54%) | 9 / 2241 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Embolism  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Embolism arterial                               |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Embolism venous                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive crisis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypotension                                     |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intermittent claudication                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphocele                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphoedema                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Phlebitis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shock   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian vein thrombosis                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Superior vena cava syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis superficial                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varicose vein                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vena cava thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Venous thrombosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Ankle arthroplasty                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast conserving surgery                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast operation                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast reconstruction                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cancer surgery                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Catheter removal                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical polypectomy                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystectomy                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Incisional drainage                                  |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Mammoplasty  |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Oophorectomy bilateral                               |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Salpingo-oophorectomy bilateral                      |                  |                  |  |
| subjects affected / exposed                          | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Uterine dilation and curettage                       |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Mastectomy   |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pregnancy, puerperium and perinatal conditions       |                  |                  |  |
| Foetal death   |                  |                  |  |
| subjects affected / exposed                          | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| Adverse drug reaction                               |                  |                  |  |
| subjects affected / exposed                         | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Application site pain                               |                  |                  |  |
| subjects affected / exposed                         | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Asthenia  |                  |                  |  |
| subjects affected / exposed                         | 3 / 2218 (0.14%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all     | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| BRCA2 gene mutation                                 |                  |                  |  |
| subjects affected / exposed                         | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Breast complication associated with device          |                  |                  |  |
| subjects affected / exposed                         | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Capsular contracture associated with breast implant |                  |                  |  |
| subjects affected / exposed                         | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Catheter site haematoma                             |                  |                  |  |
| subjects affected / exposed                         | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all     | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Chest discomfort                                    |                  |                  |  |
| subjects affected / exposed                         | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all     | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0            |  |
| Chest pain  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chills  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Complication associated with device             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Death   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Disease progression                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Drug intolerance                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extravasation                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 4 / 2218 (0.18%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Generalised oedema                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Granuloma                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Idiosyncratic drug reaction                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired healing                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated hernia                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammation                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza like illness                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infusion site extravasation                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mucosal inflammation                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral swelling                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudocyst                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 33 / 2218 (1.49%) | 37 / 2241 (1.65%) |  |
| occurrences causally related to treatment / all | 1 / 40            | 4 / 42            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Immune system disorders                         |                   |                   |  |
| Drug hypersensitivity                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Allergy to vaccine                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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                     | 2 / 2218 (0.09%)  | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Reaction to preservatives                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Reproductive system and breast disorders        |                   |                   |  |
| Bartholin's cyst                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast haematoma                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast inflammation                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Breast mass                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast necrosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast pain                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical dysplasia                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystocele                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysfunctional uterine bleeding                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial disorder                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial hyperplasia                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometriosis                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic ovarian cyst                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Menometrorrhagia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Menopausal symptoms                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Menorrhagia                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metrorrhagia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 7 / 2218 (0.32%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian enlargement                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic pain                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postmenopausal haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine polyp                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory distress syndrome             |                  |                  |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Asthma  |                   |                   |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atelectasis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic obstructive pulmonary disease           |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 10 / 2218 (0.45%) | 13 / 2241 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 1 / 13            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Dyspnoea at rest                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea exertional                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Epistaxis                                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperventilation                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Interstitial lung disease                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngospasm                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung infiltration                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive airways disorder                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Organising pneumonia                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oropharyngeal pain                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 2218 (0.23%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleurisy  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 2 / 2218 (0.09%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Productive cough                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 20 / 2218 (0.90%) | 17 / 2241 (0.76%) |  |
| occurrences causally related to treatment / all | 0 / 21            | 2 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary mass                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory arrest                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Respiratory failure                             |                   |                   |  |
| subjects affected / exposed                     | 7 / 2218 (0.32%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 1 / 8             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1             |  |
| Vocal cord polyp                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Psychiatric disorders                           |                   |                   |  |
| Alcoholism                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anxiety   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 7 / 2241 (0.31%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anxiety disorder                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depressed mood                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 8 / 2241 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypomania                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Insomnia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Major depression                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mania   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Persistent depressive disorder                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychomotor retardation                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Restlessness                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicidal ideation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Device expulsion                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device failure                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary colic                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis chronic                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 4 / 2218 (0.18%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholestasis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gallbladder non-functioning                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic failure                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Hepatic function abnormal                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic steatosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatocellular injury                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatomegaly                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperbilirubinaemia                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperplastic cholecystopathy                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice cholestatic                            |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Investigations</b>                           |                  |                  |  |
| Alanine aminotransferase increased              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aspartate aminotransferase increased            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Body temperature increased                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone scan abnormal                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac murmur                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ejection fraction decreased                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrin D dimer increased                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoglobin decreased                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| International normalised ratio increased        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver function test abnormal                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutrophil count abnormal                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutrophil count decreased                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oestradiol increased                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oxygen saturation decreased                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stroke volume increased                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transaminases increased                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| White blood cell count decreased                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Abdominal wound dehiscence                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Accidental overdose                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acetabulum fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol poisoning                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cartilage injury                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Craniocerebral injury                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Exposure to radiation                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial bones fracture                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibula fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Graft complication                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incision site pain                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incisional hernia                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infusion related reaction                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intentional overdose                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament sprain                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle strain                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax traumatic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Poisoning                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural inflammation                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postmastectomy lymphoedema syndrome             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative renal failure                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative thrombosis                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound complication                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural complication                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural pain                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pubis fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation injury                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation mastitis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation pneumonitis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Scapula fracture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seroma  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin flap necrosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subarachnoid haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial rupture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tibia fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulna fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound dehiscence                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrong drug administered                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 3 / 2218 (0.14%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina pectoris                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina unstable                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriospasm coronary                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial flutter                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial thrombosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bradycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac aneurysm                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac arrest                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure chronic                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure congestive                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Cardio-respiratory arrest                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Cardiogenic shock                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiopulmonary failure                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery occlusion                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular dysfunction                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic cardiomyopathy                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myocardial infarction                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Palpitations                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pericardial effusion                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pericarditis constrictive                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus tachycardia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (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 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachyarrhythmia                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 5 / 2218 (0.23%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Aphasia   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ataxia  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain oedema                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carpal tunnel syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar ataxia                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar infarction                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral disorder                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral infarction                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cerebral ischaemia                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrospinal fistula                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrovascular accident                        |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Cervical radiculopathy                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coma hepatic                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Dementia  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia with Lewy bodies                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depressed level of consciousness                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 1            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dystonia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Epilepsy  |                  |                  |  |



|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Facial neuralgia                                |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Facial paralysis                                |                  |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Headache  |                  |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 10 / 2241 (0.45%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hemiparesis                                     |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hydrocephalus                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Intracranial aneurysm                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ischaemic stroke                                |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Lethargy  |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Loss of consciousness                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myoclonus                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurological symptom                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuropathy peripheral                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Occipital neuralgia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral sensory neuropathy                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychomotor hyperactivity                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ruptured cerebral aneurysm                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Somnolence                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Status epilepticus                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Superior sagittal sinus thrombosis              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 9 / 2218 (0.41%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombotic stroke                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Trigeminal nerve disorder                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual field defect                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| IIIrd nerve paralysis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nerve root compression                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Agranulocytosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaemia   |                  |                  |  |

|   |                    |                   |
|---|--------------------|-------------------|
| subjects affected / exposed                     | 12 / 2218 (0.54%)  | 17 / 2241 (0.76%) |
| occurrences causally related to treatment / all | 1 / 13             | 0 / 19            |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 1             |
| Anaemia megaloblastic                           |                    |                   |
| subjects affected / exposed                     | 1 / 2218 (0.05%)   | 0 / 2241 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2              | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Bone marrow failure                             |                    |                   |
| subjects affected / exposed                     | 1 / 2218 (0.05%)   | 0 / 2241 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Febrile neutropenia                             |                    |                   |
| subjects affected / exposed                     | 114 / 2218 (5.14%) | 83 / 2241 (3.70%) |
| occurrences causally related to treatment / all | 4 / 128            | 1 / 98            |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Immune thrombocytopenic purpura                 |                    |                   |
| subjects affected / exposed                     | 0 / 2218 (0.00%)   | 1 / 2241 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Leukocytosis                                    |                    |                   |
| subjects affected / exposed                     | 3 / 2218 (0.14%)   | 0 / 2241 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Leukopenia                                      |                    |                   |
| subjects affected / exposed                     | 5 / 2218 (0.23%)   | 2 / 2241 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 6              | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Neutropenia                                     |                    |                   |
| subjects affected / exposed                     | 36 / 2218 (1.62%)  | 35 / 2241 (1.56%) |
| occurrences causally related to treatment / all | 3 / 43             | 1 / 39            |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0             |
| Pancytopenia                                    |                    |                   |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 2218 (0.23%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Deafness  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear pain  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| External ear disorder                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tinnitus  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo positional                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Angle closure glaucoma                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blindness                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 5 / 2218 (0.23%) | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 3 / 5            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diplopia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular hole                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal detachment                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinopathy proliferative                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vision blurred                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitreous haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitreous haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal incarcerated hernia                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain lower                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fissure                                    |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fistula                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal prolapse                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ulcerative                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 4 / 2241 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Crohn's disease                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dental caries                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (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                     | 24 / 2218 (1.08%) | 15 / 2241 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 25            | 2 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diverticular perforation                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diverticulum intestinal                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Duodenal obstruction                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (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                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspepsia                                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis haemorrhagic                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral hernia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric polyps                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorder                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gingival pain                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoidal haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids thrombosed                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal obstruction                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine perforation                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine polyp                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mouth ulceration                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 10 / 2218 (0.45%) | 18 / 2241 (0.80%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 2 / 24            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Necrotising colitis                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Obstructive pancreatitis                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oesophageal spasm                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oesophageal stenosis                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pancreatitis acute                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pancreatitis chronic                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rectal haemorrhage                              |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Small intestinal obstruction                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stomatitis                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Umbilical hernia                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper gastrointestinal haemorrhage              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vomiting  |                   |                   |  |
| subjects affected / exposed                     | 13 / 2218 (0.59%) | 24 / 2241 (1.07%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 2 / 31            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Angioedema                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dermatitis                                      |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erythema  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lichen sclerosus                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Onycholysis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain of skin                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash papular                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Segmented hyalinising vasculitis                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin ulcer                                      |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxic skin eruption                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urticaria                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Acute kidney injury                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder perforation                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus bladder                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysuria   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrocalcinosis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal impairment                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureteric stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Hypothyroidism                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroiditis acute                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 1 / 2218 (0.05%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 6 / 2218 (0.27%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone pain                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Flank pain                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaw disorder                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint instability                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar spinal stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal pain                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myalgia   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neck pain                                       |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteitis  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteoarthritis                                  |                  |                   |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%) | 6 / 2241 (0.27%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteochondritis                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteochondrosis                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteonecrosis                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteonecrosis of jaw                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 30 / 2241 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 29 / 31           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pain in extremity                               |                  |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pain in jaw                                     |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periarthritis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periostitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue necrosis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (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 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tenosynovitis stenosans                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendiceal abscess                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 3 / 2218 (0.14%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atypical pneumonia                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacteraemia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial sepsis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Bartholinitis                                   |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast abscess                                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 5 / 2241 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast cellulitis                               |                   |                   |  |
| subjects affected / exposed                     | 18 / 2218 (0.81%) | 20 / 2241 (0.89%) |  |
| occurrences causally related to treatment / all | 2 / 20            | 0 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis                                      |                   |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 4 / 2241 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bursitis infective                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Campylobacter gastroenteritis                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Catheter site infection                         |                   |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis                                      |                   |                   |  |
| subjects affected / exposed                     | 30 / 2218 (1.35%) | 34 / 2241 (1.52%) |  |
| occurrences causally related to treatment / all | 0 / 33            | 2 / 42            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis staphylococcal                       |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulitis streptococcal                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chest wall abscess                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridial infection                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium colitis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile colitis                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile infection                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colonic abscess                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dengue fever                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Device related infection                        |                   |                   |  |
| subjects affected / exposed                     | 10 / 2218 (0.45%) | 3 / 2241 (0.13%)  |  |
| occurrences causally related to treatment / all | 1 / 11            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Device related sepsis                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diverticulitis                                  |                   |                   |  |
| subjects affected / exposed                     | 8 / 2218 (0.36%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Erysipelas                                      |                   |                   |  |
| subjects affected / exposed                     | 4 / 2218 (0.18%)  | 14 / 2241 (0.62%) |  |
| occurrences causally related to treatment / all | 1 / 5             | 1 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Erysipelothrix infection                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Escherichia bacteraemia                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Escherichia sepsis                              |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia urinary tract infection             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile infection                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fungal skin infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis salmonella                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis viral                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital herpes simplex                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| H1N1 influenza                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemophilus infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis B                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis C                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected fistula                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected seroma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infectious colitis                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 2218 (0.23%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral discitis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Labyrinthitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection bacterial     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung infection                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphangitis                                    |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Mastitis</b>                                 |                   |                   |  |
| subjects affected / exposed                     | 8 / 2218 (0.36%)  | 12 / 2241 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Mastitis bacterial</b>                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Meningitis aseptic</b>                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Mycobacterial infection</b>                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Necrotising fasciitis</b>                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Neutropenic infection</b>                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Neutropenic sepsis</b>                       |                   |                   |  |
| subjects affected / exposed                     | 14 / 2218 (0.63%) | 15 / 2241 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Oesophageal candidiasis</b>                  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ophthalmic herpes zoster                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oral candidiasis                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis chronic                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic inflammatory disease                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pericoronitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Perirectal abscess                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal abscess                              |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Periumbilical abscess                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngeal abscess                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis                                     |                   |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis streptococcal                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 30 / 2218 (1.35%) | 27 / 2241 (1.20%) |  |
| occurrences causally related to treatment / all | 0 / 32            | 2 / 29            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia haemophilus                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia klebsiella                            |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia staphylococcal                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia streptococcal                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural cellulitis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative abscess                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 9 / 2218 (0.41%) | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomonal sepsis                              |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pyelonephritis                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 5 / 2241 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pyelonephritis acute                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Respiratory tract infection                     |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sebaceous gland infection                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sepsis  |                   |                  |  |
| subjects affected / exposed                     | 11 / 2218 (0.50%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0            |  |
| Septic shock                                    |                   |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Sinusitis                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Skin infection                                  |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal infection                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 4 / 2241 (0.18%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal skin infection                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal sepsis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous abscess                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth infection                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheobronchitis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (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                     | 9 / 2218 (0.41%)  | 7 / 2241 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Upper respiratory tract infection bacterial     |                   |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Urinary tract infection                         |                   |                  |  |
| subjects affected / exposed                     | 13 / 2218 (0.59%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Urinary tract infection bacterial               |                   |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%)  | 2 / 2241 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Urinary tract infection pseudomonal             |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Urosepsis                                       |                   |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%)  | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vestibular neuronitis                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%)  | 1 / 2241 (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 / 2218 (0.09%)  | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Viral upper respiratory tract infection         |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vulval abscess</b>                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vulvovaginal candidiasis</b>                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Wound infection</b>                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Wound infection bacterial</b>                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Wound infection staphylococcal</b>           |                  |                  |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cystitis escherichia</b>                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Metabolism and nutrition disorders</b>       |                  |                  |  |
| <b>Decreased appetite</b>                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 3 / 2241 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Dehydration</b>                              |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 8 / 2218 (0.36%) | 16 / 2241 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Diabetes mellitus                               |                  |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 2 / 2241 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Diabetes mellitus inadequate control            |                  |                   |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Electrolyte imbalance                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fluid overload                                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hyperglycaemia                                  |                  |                   |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypocalcaemia                                   |                  |                   |  |
| subjects affected / exposed                     | 3 / 2218 (0.14%) | 5 / 2241 (0.22%)  |  |
| occurrences causally related to treatment / all | 2 / 3            | 5 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypoglycaemia                                   |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 6 / 2241 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2218 (0.05%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypophosphataemia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malnutrition                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Type 2 diabetes mellitus                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2218 (0.09%) | 0 / 2241 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitamin D deficiency                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2218 (0.00%) | 1 / 2241 (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               |  |
|---|-------------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events |                         |                         |  |
| subjects affected / exposed                           | 2123 / 2218<br>(95.72%) | 2149 / 2241<br>(95.89%) |  |
| Vascular disorders                                    |                         |                         |  |
| Hot flush   |                         |                         |  |
| subjects affected / exposed                           | 645 / 2218<br>(29.08%)  | 669 / 2241<br>(29.85%)  |  |
| occurrences (all)                                     | 859                     | 929                     |  |
| Hypertension  |                         |                         |  |
| subjects affected / exposed                           | 209 / 2218 (9.42%)      | 195 / 2241 (8.70%)      |  |
| occurrences (all)                                     | 275                     | 267                     |  |
| Lymphoedema   |                         |                         |  |
| subjects affected / exposed                           | 350 / 2218<br>(15.78%)  | 392 / 2241<br>(17.49%)  |  |
| occurrences (all)                                     | 443                     | 498                     |  |
| General disorders and administration site conditions  |                         |                         |  |
| Asthenia  |                         |                         |  |
| subjects affected / exposed                           | 404 / 2218<br>(18.21%)  | 407 / 2241<br>(18.16%)  |  |
| occurrences (all)                                     | 806                     | 796                     |  |
| Fatigue   |                         |                         |  |
| subjects affected / exposed                           | 893 / 2218<br>(40.26%)  | 901 / 2241<br>(40.21%)  |  |
| occurrences (all)                                     | 1638                    | 1724                    |  |
| Influenza like illness                                |                         |                         |  |
| subjects affected / exposed                           | 145 / 2218 (6.54%)      | 154 / 2241 (6.87%)      |  |
| occurrences (all)                                     | 220                     | 284                     |  |
| Mucosal inflammation                                  |                         |                         |  |
| subjects affected / exposed                           | 278 / 2218<br>(12.53%)  | 281 / 2241<br>(12.54%)  |  |
| occurrences (all)                                     | 372                     | 373                     |  |
| Oedema  |                         |                         |  |
| subjects affected / exposed                           | 112 / 2218 (5.05%)      | 106 / 2241 (4.73%)      |  |
| occurrences (all)                                     | 131                     | 113                     |  |
| Oedema peripheral                                     |                         |                         |  |
| subjects affected / exposed                           | 397 / 2218<br>(17.90%)  | 380 / 2241<br>(16.96%)  |  |
| occurrences (all)                                     | 534                     | 498                     |  |



|   |                        |                        |  |
|---|------------------------|------------------------|--|
| Pain  |                        |                        |  |
| subjects affected / exposed                     | 178 / 2218 (8.03%)     | 156 / 2241 (6.96%)     |  |
| occurrences (all)                               | 210                    | 190                    |  |
| Pyrexia   |                        |                        |  |
| subjects affected / exposed                     | 342 / 2218<br>(15.42%) | 338 / 2241<br>(15.08%) |  |
| occurrences (all)                               | 474                    | 458                    |  |
| Reproductive system and breast disorders        |                        |                        |  |
| Breast pain                                     |                        |                        |  |
| subjects affected / exposed                     | 189 / 2218 (8.52%)     | 178 / 2241 (7.94%)     |  |
| occurrences (all)                               | 218                    | 236                    |  |
| Respiratory, thoracic and mediastinal disorders |                        |                        |  |
| Cough   |                        |                        |  |
| subjects affected / exposed                     | 426 / 2218<br>(19.21%) | 410 / 2241<br>(18.30%) |  |
| occurrences (all)                               | 549                    | 557                    |  |
| Dyspnoea  |                        |                        |  |
| subjects affected / exposed                     | 268 / 2218<br>(12.08%) | 280 / 2241<br>(12.49%) |  |
| occurrences (all)                               | 363                    | 369                    |  |
| Epistaxis                                       |                        |                        |  |
| subjects affected / exposed                     | 151 / 2218 (6.81%)     | 168 / 2241 (7.50%)     |  |
| occurrences (all)                               | 176                    | 192                    |  |
| Oropharyngeal pain                              |                        |                        |  |
| subjects affected / exposed                     | 176 / 2218 (7.94%)     | 157 / 2241 (7.01%)     |  |
| occurrences (all)                               | 199                    | 186                    |  |
| Psychiatric disorders                           |                        |                        |  |
| Anxiety   |                        |                        |  |
| subjects affected / exposed                     | 207 / 2218 (9.33%)     | 220 / 2241 (9.82%)     |  |
| occurrences (all)                               | 248                    | 277                    |  |
| Depression                                      |                        |                        |  |
| subjects affected / exposed                     | 202 / 2218 (9.11%)     | 195 / 2241 (8.70%)     |  |
| occurrences (all)                               | 245                    | 236                    |  |
| Insomnia  |                        |                        |  |
| subjects affected / exposed                     | 432 / 2218<br>(19.48%) | 429 / 2241<br>(19.14%) |  |
| occurrences (all)                               | 531                    | 538                    |  |
| Investigations                                  |                        |                        |  |

|   |                            |                            |  |
|---|----------------------------|----------------------------|--|
| Weight increased<br>subjects affected / exposed<br>occurrences (all)              | 151 / 2218 (6.81%)<br>236  | 167 / 2241 (7.45%)<br>296  |  |
| Injury, poisoning and procedural complications                                    |                            |                            |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)               | 161 / 2218 (7.26%)<br>237  | 170 / 2241 (7.59%)<br>231  |  |
| Radiation skin injury<br>subjects affected / exposed<br>occurrences (all)         | 351 / 2218 (15.83%)<br>419 | 361 / 2241 (16.11%)<br>432 |  |
| Nervous system disorders  |                            |                            |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                     | 255 / 2218 (11.50%)<br>336 | 273 / 2241 (12.18%)<br>367 |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                     | 344 / 2218 (15.51%)<br>460 | 351 / 2241 (15.66%)<br>473 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                      | 567 / 2218 (25.56%)<br>957 | 527 / 2241 (23.52%)<br>844 |  |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                 | 112 / 2218 (5.05%)<br>137  | 112 / 2241 (5.00%)<br>156  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)         | 421 / 2218 (18.98%)<br>576 | 417 / 2241 (18.61%)<br>584 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                  | 197 / 2218 (8.88%)<br>254  | 216 / 2241 (9.64%)<br>271  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 177 / 2218 (7.98%)<br>249  | 198 / 2241 (8.84%)<br>289  |  |
| Blood and lymphatic system disorders  |                            |                            |  |
| Anaemia   |                            |                            |  |

|                             |                         |                         |  |
|-----------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed | 349 / 2218<br>(15.73%)  | 354 / 2241<br>(15.80%)  |  |
| occurrences (all)           | 677                     | 664                     |  |
| Leukopenia                  |                         |                         |  |
| subjects affected / exposed | 154 / 2218 (6.94%)      | 145 / 2241 (6.47%)      |  |
| occurrences (all)           | 338                     | 319                     |  |
| Neutropenia                 |                         |                         |  |
| subjects affected / exposed | 461 / 2218<br>(20.78%)  | 441 / 2241<br>(19.68%)  |  |
| occurrences (all)           | 826                     | 920                     |  |
| Eye disorders               |                         |                         |  |
| Lacrimation increased       |                         |                         |  |
| subjects affected / exposed | 243 / 2218<br>(10.96%)  | 195 / 2241 (8.70%)      |  |
| occurrences (all)           | 276                     | 218                     |  |
| Gastrointestinal disorders  |                         |                         |  |
| Abdominal pain              |                         |                         |  |
| subjects affected / exposed | 242 / 2218<br>(10.91%)  | 232 / 2241<br>(10.35%)  |  |
| occurrences (all)           | 320                     | 296                     |  |
| Abdominal pain upper        |                         |                         |  |
| subjects affected / exposed | 199 / 2218 (8.97%)      | 179 / 2241 (7.99%)      |  |
| occurrences (all)           | 248                     | 218                     |  |
| Constipation                |                         |                         |  |
| subjects affected / exposed | 635 / 2218<br>(28.63%)  | 626 / 2241<br>(27.93%)  |  |
| occurrences (all)           | 958                     | 903                     |  |
| Diarrhoea                   |                         |                         |  |
| subjects affected / exposed | 638 / 2218<br>(28.76%)  | 660 / 2241<br>(29.45%)  |  |
| occurrences (all)           | 1011                    | 1112                    |  |
| Dyspepsia                   |                         |                         |  |
| subjects affected / exposed | 245 / 2218<br>(11.05%)  | 273 / 2241<br>(12.18%)  |  |
| occurrences (all)           | 317                     | 367                     |  |
| Nausea                      |                         |                         |  |
| subjects affected / exposed | 1095 / 2218<br>(49.37%) | 1145 / 2241<br>(51.09%) |  |
| occurrences (all)           | 2210                    | 2327                    |  |
| Stomatitis                  |                         |                         |  |
| subjects affected / exposed | 398 / 2218<br>(17.94%)  | 399 / 2241<br>(17.80%)  |  |
| occurrences (all)           | 596                     | 624                     |  |

|  |                                |                                |  |
|--|--------------------------------|--------------------------------|--|
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | 159 / 2218 (7.17%)<br>184      | 198 / 2241 (8.84%)<br>236      |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 536 / 2218<br>(24.17%)<br>865  | 536 / 2241<br>(23.92%)<br>882  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all) | 923 / 2218<br>(41.61%)<br>1129 | 938 / 2241<br>(41.86%)<br>1158 |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)   | 112 / 2218 (5.05%)<br>132      | 107 / 2241 (4.77%)<br>134      |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)   | 133 / 2218 (6.00%)<br>143      | 125 / 2241 (5.58%)<br>145      |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)   | 226 / 2218<br>(10.19%)<br>255  | 260 / 2241<br>(11.60%)<br>315  |  |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all)                                      | 264 / 2218<br>(11.90%)<br>303  | 275 / 2241<br>(12.27%)<br>328  |  |
| Palmar-plantar erythrodysaesthesia<br>syndrome<br>subjects affected / exposed<br>occurrences (all)     | 114 / 2218 (5.14%)<br>152      | 138 / 2241 (6.16%)<br>201      |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 181 / 2218 (8.16%)<br>223      | 144 / 2241 (6.43%)<br>159      |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 372 / 2218<br>(16.77%)<br>514  | 392 / 2241<br>(17.49%)<br>540  |  |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia                                       |                                |                                |  |

|                             |                        |                        |  |
|-----------------------------|------------------------|------------------------|--|
| subjects affected / exposed | 974 / 2218<br>(43.91%) | 973 / 2241<br>(43.42%) |  |
| occurrences (all)           | 1799                   | 1787                   |  |
| Back pain                   |                        |                        |  |
| subjects affected / exposed | 486 / 2218<br>(21.91%) | 563 / 2241<br>(25.12%) |  |
| occurrences (all)           | 657                    | 823                    |  |
| Bone pain                   |                        |                        |  |
| subjects affected / exposed | 256 / 2218<br>(11.54%) | 288 / 2241<br>(12.85%) |  |
| occurrences (all)           | 342                    | 422                    |  |
| Muscle spasms               |                        |                        |  |
| subjects affected / exposed | 204 / 2218 (9.20%)     | 201 / 2241 (8.97%)     |  |
| occurrences (all)           | 247                    | 253                    |  |
| Musculoskeletal chest pain  |                        |                        |  |
| subjects affected / exposed | 143 / 2218 (6.45%)     | 129 / 2241 (5.76%)     |  |
| occurrences (all)           | 179                    | 154                    |  |
| Musculoskeletal pain        |                        |                        |  |
| subjects affected / exposed | 308 / 2218<br>(13.89%) | 337 / 2241<br>(15.04%) |  |
| occurrences (all)           | 431                    | 444                    |  |
| Myalgia                     |                        |                        |  |
| subjects affected / exposed | 539 / 2218<br>(24.30%) | 553 / 2241<br>(24.68%) |  |
| occurrences (all)           | 838                    | 910                    |  |
| Neck pain                   |                        |                        |  |
| subjects affected / exposed | 112 / 2218 (5.05%)     | 106 / 2241 (4.73%)     |  |
| occurrences (all)           | 132                    | 118                    |  |
| Pain in extremity           |                        |                        |  |
| subjects affected / exposed | 545 / 2218<br>(24.57%) | 570 / 2241<br>(25.44%) |  |
| occurrences (all)           | 815                    | 871                    |  |
| Pain in jaw                 |                        |                        |  |
| subjects affected / exposed | 124 / 2218 (5.59%)     | 150 / 2241 (6.69%)     |  |
| occurrences (all)           | 146                    | 182                    |  |
| Infections and infestations |                        |                        |  |
| Bronchitis                  |                        |                        |  |
| subjects affected / exposed | 112 / 2218 (5.05%)     | 86 / 2241 (3.84%)      |  |
| occurrences (all)           | 134                    | 112                    |  |
| Influenza                   |                        |                        |  |

|                                    |                        |                        |  |
|------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed        | 117 / 2218 (5.28%)     | 117 / 2241 (5.22%)     |  |
| occurrences (all)                  | 143                    | 138                    |  |
| Nasopharyngitis                    |                        |                        |  |
| subjects affected / exposed        | 290 / 2218<br>(13.07%) | 292 / 2241<br>(13.03%) |  |
| occurrences (all)                  | 521                    | 486                    |  |
| Sinusitis                          |                        |                        |  |
| subjects affected / exposed        | 101 / 2218 (4.55%)     | 113 / 2241 (5.04%)     |  |
| occurrences (all)                  | 136                    | 149                    |  |
| Upper respiratory tract infection  |                        |                        |  |
| subjects affected / exposed        | 195 / 2218 (8.79%)     | 206 / 2241 (9.19%)     |  |
| occurrences (all)                  | 265                    | 283                    |  |
| Urinary tract infection            |                        |                        |  |
| subjects affected / exposed        | 149 / 2218 (6.72%)     | 177 / 2241 (7.90%)     |  |
| occurrences (all)                  | 211                    | 252                    |  |
| Metabolism and nutrition disorders |                        |                        |  |
| Decreased appetite                 |                        |                        |  |
| subjects affected / exposed        | 289 / 2218<br>(13.03%) | 330 / 2241<br>(14.73%) |  |
| occurrences (all)                  | 427                    | 486                    |  |
| Hypocalcaemia                      |                        |                        |  |
| subjects affected / exposed        | 73 / 2218 (3.29%)      | 135 / 2241 (6.02%)     |  |
| occurrences (all)                  | 95                     | 181                    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 05 May 2011     | <ul style="list-style-type: none"><li>- window for screening imaging assessments to document disease extent was increased from 12 to 24 weeks</li><li>- a second formal interim analysis was added in consideration of the length of time anticipated to reach the primary analysis date</li><li>- amount of time expected to reach the primary analysis data cutoff date was modified</li><li>- number of centers was increased from 400 to 500 centers globally</li><li>- breast density measurements were included as an exploratory outcome (objective and endpoint) for the study</li></ul>   |
| 15 August 2012  | <ul style="list-style-type: none"><li>- collection of skeletal-related event information was extended through the long-term follow-up</li><li>- objectives and endpoints for skeletal-related events and bone metastasis were modified</li><li>- fasting requirement from the urine collection for urinary N-telopeptide of type I collagen was removed</li></ul>  |
| 18 March 2015   | <ul style="list-style-type: none"><li>- disease-free survival in the postmenopausal subset as a secondary endpoint was added</li><li>- hazard ratio of denosumab compared with placebo was added for the postmenopausal subset</li><li>- pathological variables in tumor tissue from neoadjuvant subjects after surgery was added as an exploratory objective</li><li>- numbers of subjects with events (any disease recurrence or died, whichever comes last) required for the interim and final analyses was updated</li><li>- period of time for which subjects must not become pregnant or breastfeed after the end of treatment was updated</li><li>- duration of the study was changed based on the change in the expected/projected time to primary analysis</li><li>- atypical femoral fracture was included as an adverse event of interest with adjudication by an independent panel of experts</li><li>- covariates explored in relation to the primary and secondary efficacy endpoints were updated; primary tumor size and lymph node status were added to the list of covariates</li><li>- expected event rates at 3 years for bone metastasis-free survival and disease-free survival were updated</li></ul> |
| 17 October 2016 | <ul style="list-style-type: none"><li>- primary analysis was changed from an event-driven analysis to a landmark (time-based) analysis, triggered when all subjects had the opportunity to complete 5 years treatment with investigational product</li><li>- second interim analysis from the study was removed</li><li>- open-label phase from the study was removed</li><li>- long-term follow-up visit frequency and assessments before and after the primary analysis cutoff date was redefined</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

