



## Clinical trial results:

**A randomized, multi-center Phase IIIb, open label, study of letrozole vs anastrozole in the adjuvant treatment of postmenopausal women with hormone receptor and node positive breast cancer**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.**

## Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2005-004263-35                |
| Trial protocol           | IE FI ES SE GB AT DK BE DE IT |
| Global end of trial date | 08 September 2014             |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 06 July 2018 |
| First version publication date | 06 July 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CFEM345D2411 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00248170 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 08 September 2014 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 08 September 2014 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to compare the rate of disease-free survival (DFS) when 959 DFS events had occurred in postmenopausal women with hormone receptor and lymph node positive breast cancer randomized between letrozole and anastrozole.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 07 December 2005 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy         |
| Long term follow-up duration                              | 3 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 301         |
| Country: Number of subjects enrolled | Austria: 198           |
| Country: Number of subjects enrolled | Belgium: 139           |
| Country: Number of subjects enrolled | Canada: 124            |
| Country: Number of subjects enrolled | China: 38              |
| Country: Number of subjects enrolled | Denmark: 270           |
| Country: Number of subjects enrolled | Finland: 21            |
| Country: Number of subjects enrolled | France: 206            |
| Country: Number of subjects enrolled | Germany: 358           |
| Country: Number of subjects enrolled | Ireland: 165           |
| Country: Number of subjects enrolled | Israel: 103            |
| Country: Number of subjects enrolled | Italy: 305             |
| Country: Number of subjects enrolled | Japan: 297             |
| Country: Number of subjects enrolled | Korea, Republic of: 30 |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Netherlands: 85     |
| Country: Number of subjects enrolled | New Zealand: 65     |
| Country: Number of subjects enrolled | Norway: 13          |
| Country: Number of subjects enrolled | Spain: 104          |
| Country: Number of subjects enrolled | Sweden: 59          |
| Country: Number of subjects enrolled | Switzerland: 20     |
| Country: Number of subjects enrolled | United Kingdom: 282 |
| Country: Number of subjects enrolled | United States: 953  |
| Worldwide total number of subjects   | 4136                |
| EEA total number of subjects         | 2205                |

Notes:

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### 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)                      | 2490 |
| From 65 to 84 years                       | 1646 |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants, who had recently undergone surgery, were randomly assigned in 1:1 ratio to letrozole or anastrozole. Participants received daily treatment until disease recurrence/relapse or for a maximum of 5 years. Participants underwent post-treatment long term follow-up for disease-free survival and overall survival.

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

Arm description:

2.5 mg by mouth (p.o.) once daily

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

Dosage and administration details:

2.5 mg orally once a day

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

Arm description:

1 mg p.o. once daily

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

Dosage and administration details:

1 mg orally once a day

| <b>Number of subjects in period 1</b> | Letrozole | Anastrozole |
|---------------------------------------|-----------|-------------|
| Started                               | 2061      | 2075        |
| Intent-to-treat (ITT)                 | 2061      | 2075        |
| Safety set                            | 2049      | 2062        |
| Completed                             | 1317      | 1286        |
| Not completed                         | 744       | 789         |
| Adverse event, serious fatal          | 28        | 47          |
| Consent withdrawn by subject          | 71        | 79          |
| Disease progression                   | 196       | 216         |
| Abnormal test procedure(s) result     | 49        | 61          |
| Adverse event, non-fatal              | 311       | 296         |
| Administrative problems               | 22        | 25          |
| Abnormal laboratory values            | 4         | -           |
| Lost to follow-up                     | 28        | 35          |
| Protocol deviation                    | 35        | 30          |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Letrozole |
|-----------------------|-----------|

Reporting group description:

2.5 mg by mouth (p.o.) once daily

|                       |             |
|-----------------------|-------------|
| Reporting group title | Anastrozole |
|-----------------------|-------------|

Reporting group description:

1 mg p.o. once daily

| Reporting group values                                | Letrozole | Anastrozole | Total |
|---|-----------|-------------|-------|
| Number of subjects                                    | 2061      | 2075        | 4136  |
| Age categorical<br>Units: Subjects                    |           |             |       |
| In utero  | 0         | 0           | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0         | 0           | 0     |
| Newborns (0-27 days)                                  | 0         | 0           | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0         | 0           | 0     |
| Children (2-11 years)                                 | 0         | 0           | 0     |
| Adolescents (12-17 years)                             | 0         | 0           | 0     |
| Adults (18-64 years)                                  | 1236      | 1254        | 2490  |
| From 65-84 years                                      | 806       | 802         | 1608  |
| 85 years and over                                     | 19        | 19          | 38    |
| Age Continuous  <br>Units: Years                      |           |             |       |
| arithmetic mean                                       | 63.2      | 63.1        |       |
| standard deviation                                    | ± 8.48    | ± 8.45      | -     |
| Gender categorical<br>Units: Subjects                 |           |             |       |
| Female  | 2061      | 2075        | 4136  |
| Male  | 0         | 0           | 0     |
| Gender, Customized<br>Units: Subjects                 |           |             |       |
| Female  | 2061      | 2075        | 4136  |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Letrozole   |
| Reporting group description:<br>2.5 mg by mouth (p.o.) once daily |             |
| Reporting group title   | Anastrozole |
| Reporting group description:<br>1 mg p.o. once daily              |             |

### Primary: Disease free survival

|   |                       |
|---|-----------------------|
| End point title   | Disease free survival |
| End point description:<br>Disease-free survival was defined as the time from the date of randomization to the date of the first documentation of re-occurrence of invasive breast cancer in local, regional or distant sites, new invasive breast cancer in the contra-lateral breast, or death from any cause. |                       |
| End point type  | Primary               |
| End point timeframe:<br>84 months   |                       |

| End point values             | Letrozole          | Anastrozole       |  |  |
|------------------------------|--------------------|-------------------|--|--|
| Subject group type           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed  | 2061               | 2075              |  |  |
| Units: Months                |                    |                   |  |  |
| median (confidence interval) | 999 (84.14 to 999) | 999 (-999 to 999) |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | Disease free survival   |
| Comparison groups                       | Anastrozole v Letrozole |
| Number of subjects included in analysis | 4136                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.315                 |
| Method                                  | Logrank                 |

### Secondary: Overall survival

|   |                  |
|---|------------------|
| End point title   | Overall survival |
| End point description:<br>Overall survival was defined as the time from the date of randomization to the date of death from any |                  |

cause.

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

| End point values             | Letrozole         | Anastrozole       |  |  |
|------------------------------|-------------------|-------------------|--|--|
| Subject group type           | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed  | 2061              | 2075              |  |  |
| Units: Months                |                   |                   |  |  |
| median (confidence interval) | 999 (-999 to 999) | 999 (-999 to 999) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to development of distant metastases

|   |   |
|---|---|
| End point title   | Time to development of distant metastases |
| End point description:  |   |
| Time to development of distant metastases was defined as the time from date of randomization to the date of the first development of any recurrent or metastatic disease in sites other than the local mastectomy scar, the ipsilateral breast in case of breast conservation or the contra lateral breast. |   |
| End point type  | Secondary                                 |
| End point timeframe:  |   |
| 84 months   |   |

| End point values             | Letrozole          | Anastrozole       |  |  |
|------------------------------|--------------------|-------------------|--|--|
| Subject group type           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed  | 2061               | 2075              |  |  |
| Units: Months                |                    |                   |  |  |
| median (confidence interval) | 999 (84.14 to 999) | 999 (-999 to 999) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to development of contra lateral breast cancer

|  |   |
|--|---|
| End point title  | Time to development of contra lateral breast cancer |
| End point description:   |   |
| Time to development of contra lateral breast cancer was defined as the time from the date of randomization to the date of the first development of any disease in the contra lateral breast. |   |



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

| End point values             | Letrozole         | Anastrozole       |  |  |
|------------------------------|-------------------|-------------------|--|--|
| Subject group type           | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed  | 2061              | 2075              |  |  |
| Units: Months                |                   |                   |  |  |
| median (confidence interval) | 999 (-999 to 999) | 999 (-999 to 999) |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Distant disease-free survival

|   |                               |
|---|-------------------------------|
| End point title   | Distant disease-free survival |
| End point description:  |                               |
| Distant disease-free survival was defined as the time from date of randomization to the date of the first development of any relapse at a distant site or death from any cause. |                               |
| End point type  | Secondary                     |
| End point timeframe:  |                               |
| 84 months   |                               |

| End point values             | Letrozole          | Anastrozole       |  |  |
|------------------------------|--------------------|-------------------|--|--|
| Subject group type           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed  | 2061               | 2075              |  |  |
| Units: Months                |                    |                   |  |  |
| median (confidence interval) | 999 (84.14 to 999) | 999 (-999 to 999) |  |  |

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Change from baseline in serum lipid profiles

|  |  |
|--|--|
| End point title  | Change from baseline in serum lipid profiles |
| End point description:   |  |
| Total cholesterol was analyzed to assess the impact on serum lipids profiles. The adjusted means was calculated. |  |
| End point type   | Secondary                                    |

End point timeframe:  
baseline, 6, 12, 24, 36, 48 and 60 months

| End point values                      | Letrozole              | Anastrozole            |  |  |
|---------------------------------------|------------------------|------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed           | 2049                   | 2062                   |  |  |
| Units: mg/dL                          |                        |                        |  |  |
| arithmetic mean (confidence interval) |                        |                        |  |  |
| 6 months                              | 5.643 (5.584 to 5.701) | 5.553 (5.495 to 5.611) |  |  |
| 12 months                             | 5.569 (5.51 to 5.629)  | 5.511 (5.452 to 5.57)  |  |  |
| 24 months                             | 5.508 (5.445 to 5.572) | 5.436 (5.373 to 5.499) |  |  |
| 36 months                             | 5.429 (5.359 to 5.5)   | 5.427 (5.357 to 5.497) |  |  |
| 48 months                             | 5.395 (5.323 to 5.468) | 5.366 (5.293 to 5.438) |  |  |
| 60 months                             | 5.375 (5.3 to 5.451)   | 5.368 (5.292 to 5.443) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants who experienced clinical fracture events

|                 |   |
|-----------------|---|
| End point title | Percentage of participants who experienced clinical fracture events |
|-----------------|---|

End point description:

The incidence of clinical fractures was analyzed.

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

End point timeframe:

84 months

| End point values                  | Letrozole       | Anastrozole     |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 2049            | 2062            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 9.3             | 8.1             |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of participants who experienced cardiovascular events**

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|                 |  |
|-----------------|--|
| End point title | Percentage of participants who experienced cardiovascular events |
|-----------------|--|

End point description:

The incidence of ischemic heart disease, cardiac failures, cerebrovascular accidents and thromboembolic events was analyzed.

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

End point timeframe:

84 months

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| End point values                  | Letrozole       | Anastrozole     |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 2049            | 2062            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           |                 |                 |  |  |
| Ischemic heart disease            | 2.4             | 1.5             |  |  |
| Cardiac failures                  | 1.5             | 0.7             |  |  |
| Cerebrovascular accidents         | 1.6             | 1.5             |  |  |
| Thromboembolic events             | 1.2             | 1.2             |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Anastrozole |
|-----------------------|-------------|

Reporting group description:

Anastrozole

|                       |           |
|-----------------------|-----------|
| Reporting group title | Letrozole |
|-----------------------|-----------|

Reporting group description:

Letrozole

| Serious adverse events  | Anastrozole            | Letrozole              |  |
|---|------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                        |                        |  |
| subjects affected / exposed   | 520 / 2062<br>(25.22%) | 485 / 2049<br>(23.67%) |  |
| number of deaths (all causes)                                       | 46                     | 42                     |  |
| number of deaths resulting from adverse events                      | 2                      | 1                      |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |  |
| Adenocarcinoma of colon   |                        |                        |  |
| subjects affected / exposed   | 1 / 2062 (0.05%)       | 2 / 2049 (0.10%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 2                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Adenocarcinoma of the cervix  |                        |                        |  |
| subjects affected / exposed   | 1 / 2062 (0.05%)       | 0 / 2049 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 1 / 1                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Angiomyolipoma  |                        |                        |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign laryngeal neoplasm                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign lymph node neoplasm                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign neoplasm of thyroid gland                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign salivary gland neoplasm                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone cancer                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Breast cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibroma   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibromatosis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder cancer                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal carcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastrointestinal tract adenoma                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glioblastoma multiforme                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemangioma                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lip and/or oral cavity cancer                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lip neoplasm benign                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung neoplasm malignant                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lymphangiosis carcinomatosa                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma in situ                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant neoplasm progression                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant peritoneal neoplasm                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningioma                                      |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to abdominal cavity                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to bone                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to central nervous system            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to peritoneum                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastatic pain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurilemmoma benign                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-small cell lung cancer                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer stage III                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Ovarian fibroma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pituitary tumour benign                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleomorphic adenoma                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenoma                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectosigmoid cancer                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Retro-orbital neoplasm                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland neoplasm                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schwannoma                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seborrhoeic keratosis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Signet-ring cell carcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Squamous cell carcinoma                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of skin                 |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                      | 4 / 2062 (0.19%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Superficial spreading melanoma stage unspecified |                  |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Thyroid adenoma                                  |                  |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Thyroid neoplasm                                 |                  |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Uterine leiomyoma                                |                  |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Waldenstrom's macroglobulinaemia                 |                  |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| Vascular disorders                               |                  |                  |  |
| Aortic aneurysm                                  |                  |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all  | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 1            |  |
| Aortic aneurysm rupture                          |                  |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 1            |  |
| Aortic dissection                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Aortic stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic thrombosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arterial disorder                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arterial occlusive disease                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriosclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Capillary fragility                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 2062 (0.39%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 2 / 8            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Embolism  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extremity necrosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhage                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 7 / 2049 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive crisis                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypotension                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hypovolaemic shock                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iliac artery occlusion                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intra-abdominal haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphocele                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphoedema                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral venous disease                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Temporal arteritis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thromboangiitis obliterans                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varicose vein                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vena cava thrombosis                            |                  |                  |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Venous thrombosis limb                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Surgical and medical procedures                 |                   |                   |  |
| Breast lump removal                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast operation                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast prosthesis implantation                  |                   |                   |  |
| subjects affected / exposed                     | 10 / 2062 (0.48%) | 5 / 2049 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast prosthesis removal                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Breast reconstruction                           |                   |                   |  |
| subjects affected / exposed                     | 16 / 2062 (0.78%) | 24 / 2049 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 27            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Central venous catheter removal                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Knee arthroplasty                               |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mammoplasty                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mastectomy                                      |                  |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mechanical ventilation                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Medical device removal                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus removal                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Modified radical mastectomy                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Removal of internal fixation                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Scar excision                                   |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Spinal laminectomy                                   |                  |                  |  |
| subjects affected / exposed                          | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Wound treatment                                      |                  |                  |  |
| subjects affected / exposed                          | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Asthenia   |                  |                  |  |
| subjects affected / exposed                          | 6 / 2062 (0.29%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 6            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Cardiac death  |                  |                  |  |
| subjects affected / exposed                          | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 2            |  |
| Chest discomfort                                     |                  |                  |  |
| subjects affected / exposed                          | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Chest pain   |                  |                  |  |
| subjects affected / exposed                          | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Death  |                  |                  |  |
| subjects affected / exposed                          | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 2            | 0 / 2            |  |
| Device damage  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device dislocation                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Disease progression                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Disease recurrence                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drowning  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Fat necrosis                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gait disturbance                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired healing                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Implant site extravasation                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injection site phlebitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malaise   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multi-organ failure                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patient-device incompatibility                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                     | 8 / 2062 (0.39%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden death                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Thrombosis in device                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Anaphylactic shock                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug hypersensitivity                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypersensitivity                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sarcoidosis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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        |                  |                  |  |
| Adnexa uteri mass                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anisomastia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast calcifications                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast fibrosis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast inflammation                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast mass                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast oedema                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colpocele                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystocele                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial hyperplasia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Female genital tract fistula                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Genital prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metrorrhagia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nipple disorder                                 |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nipple exudate bloody                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 3 / 2062 (0.15%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic prolapse                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Perineal pain                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectocele                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine fistula                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Uterine polyp                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine prolapse                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal inflammation                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aspiration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Asthma  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchial hyperreactivity                       |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bronchospasm                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Choking   |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Chronic obstructive pulmonary disease           |                  |                   |  |
| subjects affected / exposed                     | 9 / 2062 (0.44%) | 6 / 2049 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0             |  |
| Dyspnoea  |                  |                   |  |
| subjects affected / exposed                     | 7 / 2062 (0.34%) | 10 / 2049 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dyspnoea exertional                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Emphysema                                       |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Epistaxis                                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Haemoptysis                                     |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercapnia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Idiopathic pulmonary fibrosis                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleuritic pain                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia aspiration                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Productive cough                                |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary embolism                              |                   |                  |  |
| subjects affected / exposed                     | 12 / 2062 (0.58%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 4 / 12            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Pulmonary fibrosis                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary hypertension                          |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary oedema                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Respiratory distress                            |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| 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                     | 3 / 2062 (0.15%)  | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2            |  |
| Sinus congestion                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sleep apnoea syndrome                           |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Abnormal behaviour                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Agitation                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Completed suicide                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 8 / 2062 (0.39%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depressed mood                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| subjects affected / exposed                      | 11 / 2062 (0.53%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all  | 1 / 14            | 1 / 12           |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Drug dependence                                  |                   |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Intentional self-injury                          |                   |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%)  | 0 / 2049 (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 / 2062 (0.05%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Mental disorder                                  |                   |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%)  | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all  | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Mental status changes                            |                   |                  |  |
| subjects affected / exposed                      | 2 / 2062 (0.10%)  | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all  | 0 / 2             | 0 / 3            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Mood disorder due to a general medical condition |                   |                  |  |
| subjects affected / exposed                      | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Mood swings                                      |                   |                  |  |
| subjects affected / exposed                      | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all  | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Somatisation disorder                            |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Amylase increased                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aspiration pleural cavity                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biopsy breast                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biopsy lymph gland                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone density decreased                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbohydrate antigen 15-3 increased             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium test positive                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrin D dimer increased                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| International normalised ratio increased        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lipase increased                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mammogram abnormal                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mediastinal biopsy                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight decreased                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight increased                                |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Injury, poisoning and procedural complications  |                   |                   |  |
| Acetabulum fracture                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Alcohol poisoning                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Ankle fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 10 / 2062 (0.48%) | 14 / 2049 (0.68%) |  |
| occurrences causally related to treatment / all | 1 / 10            | 5 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthropod bite                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Brain contusion                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cervical vertebral fracture                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clavicle fracture                               |                   |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Compression fracture                            |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (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                     | 1 / 2062 (0.05%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Contusion                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dislocation of vertebra                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Excoriation                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Face injury                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Facial bones fracture                           |                   |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fall  |                   |                   |  |
| subjects affected / exposed                     | 13 / 2062 (0.63%) | 17 / 2049 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 1 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Femoral neck fracture                           |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibula fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Forearm fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incisional hernia                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament rupture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament sprain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple fractures                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle strain                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 3 / 2062 (0.15%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax traumatic                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural hypothyroidism                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative hernia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound complication                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pubis fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary contusion                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation pericarditis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation pneumonitis                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radiation skin injury                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 7 / 2062 (0.34%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seroma  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skull fracture                                  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue injury                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal compression fracture                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 3 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenic rupture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sternal fracture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon rupture                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thoracic vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tibia fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheal injury                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulna fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular pseudoaneurysm                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Atrial septal defect                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syndactyly                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitello-intestinal duct remnant                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac disorders                               |                  |                  |  |
| Acute coronary syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute myocardial infarction                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Adams-Stokes syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Angina pectoris                                 |                   |                   |  |
| subjects affected / exposed                     | 8 / 2062 (0.39%)  | 8 / 2049 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina unstable                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arrhythmia                                      |                   |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Atrial fibrillation                             |                   |                   |  |
| subjects affected / exposed                     | 15 / 2062 (0.73%) | 19 / 2049 (0.93%) |  |
| occurrences causally related to treatment / all | 1 / 15            | 1 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| 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 / 2062 (0.05%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bundle branch block                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             |  |
| Cardiac disorder                                |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 4            |  |
| Cardiac failure acute                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure chronic                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure congestive                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac fibrillation                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac tamponade                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac valve disease                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardio-respiratory arrest                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Cardiomyopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiovascular insufficiency                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Conduction disorder                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congestive cardiomyopathy                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cor pulmonale                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Coronary artery disease                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 7 / 2049 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrocardiac syndrome                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic cardiomyopathy                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular dysfunction                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular failure                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mitral valve disease                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mitral valve incompetence                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.19%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Myocardial ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Palpitations                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Restrictive cardiomyopathy                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sick sinus syndrome                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stress cardiomyopathy                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachyarrhythmia                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tricuspid valve incompetence                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular extrasystoles                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                        |                  |                  |  |
| Amnesia   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ataxia  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Balance disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carpal tunnel syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 4 / 7            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral amyloid angiopathy                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cerebral infarction                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral ischaemia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| 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                     | 5 / 2062 (0.24%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 3 / 9            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Cervicobrachial syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Convulsion                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia Alzheimer's type                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysarthria                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial paresis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhage intracranial                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 2 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Horner's syndrome                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoaesthesia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intracranial aneurysm                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypogeusia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic stroke                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar radiculopathy                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Monoplegia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple sclerosis                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple sclerosis relapse                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myasthenia gravis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic neuritis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinsonism                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial seizures                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Petit mal epilepsy                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sciatica  |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sensory loss                                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Speech disorder                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Spinal claudication                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Spinal epidural haemorrhage                     |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| 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                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1             |  |
| Syncope   |                  |                   |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 13 / 2049 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Tardive dyskinesia                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Transient global amnesia                        |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 2 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tremor  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Trigeminal neuralgia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VIIth nerve paralysis                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertebrobasilar insufficiency                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Autoimmune haemolytic anaemia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic anaemia                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Hearing impaired                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inner ear disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tinnitus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tympanic membrane perforation                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 1 / 2062 (0.05%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo positional                              |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Cataract  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dacryostenosis acquired                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diplopia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glaucoma  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lens dislocation                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Macular hole                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Open angle glaucoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal vein thrombosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vision blurred                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal adhesions                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal distension                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain lower                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 7 / 2062 (0.34%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 7            | 2 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal wall haematoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal sphincter atony                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis microscopic                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Crohn's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 2 / 6            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysphagia                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocutaneous fistula                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterovesical fistula                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faecal incontinence                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faeces discoloured                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral hernia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer perforation                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis erosive                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorder                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematemesis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus paralytic                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammatory bowel disease                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal dilatation                           |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intestinal obstruction                          |                  |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 3 / 2049 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intestinal perforation                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intestinal polyp                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Large intestine polyp                           |                  |                   |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 7 / 2049 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Melaena   |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Mouth cyst                                      |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Nausea  |                  |                   |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 11 / 2049 (0.54%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 2 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Oesophagitis                                    |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spigelian hernia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stomatitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subileus  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth loss                                      |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Umbilical hernia                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Volvulus  |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 6 / 2062 (0.29%) | 11 / 2049 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hepatobiliary disorders                         |                  |                   |  |
| Biliary colic                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cholecystitis                                   |                  |                   |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 7 / 2049 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cholecystitis acute                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cholecystitis chronic                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cholelithiasis                                  |                  |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 11 / 2062 (0.53%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cholestasis                                     |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Gallbladder perforation                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Gallbladder polyp                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatic cirrhosis                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatic function abnormal                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hepatic steatosis                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Liver disorder                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                   |                  |  |
| Alopecia  |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermal cyst                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erythema multiforme                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erythrodermic psoriasis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertrophic scar                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Keloid scar                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pruritus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash maculo-papular                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin lesion                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin necrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urticaria chronic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Calculus bladder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus ureteric                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Calculus urinary                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertonic bladder                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrolithiasis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyuria  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 7 / 2062 (0.34%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Renal failure acute                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure chronic                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal impairment                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stress urinary incontinence                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral caruncle                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral obstruction                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 4 / 2062 (0.19%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract obstruction                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Autoimmune thyroiditis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Goitre  |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hyperparathyroidism                             |                   |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hypothyroidism                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Toxic nodular goitre                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                   |                  |  |
| Arthralgia                                      |                   |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%)  | 9 / 2049 (0.44%) |  |
| occurrences causally related to treatment / all | 5 / 6             | 3 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Arthritis                                       |                   |                  |  |
| subjects affected / exposed                     | 9 / 2062 (0.44%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 10            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Back pain                                       |                   |                  |  |
| subjects affected / exposed                     | 10 / 2062 (0.48%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 10            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bone pain                                       |                   |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Compartment syndrome                            |                   |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Costochondritis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot deformity                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |
| subjects affected / exposed                     | 6 / 2062 (0.29%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint instability                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint stiffness                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kyphosis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Loose body in joint                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle atrophy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal chest pain                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal pain                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal stiffness                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myalgia   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myopathy  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoarthritis                                  |                   |                   |  |
| subjects affected / exposed                     | 15 / 2062 (0.73%) | 21 / 2049 (1.02%) |  |
| occurrences causally related to treatment / all | 1 / 15            | 0 / 26            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteonecrosis                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteopenia                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoporosis                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 3 / 2049 (0.15%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 2 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Polyarthritis                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pseudarthrosis                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rheumatoid arthritis                            |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rotator cuff syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal column stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal osteoarthritis                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal pain                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylolisthesis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial cyst                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovitis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tenosynovitis                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Trigger finger                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess neck                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess soft tissue                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis infective                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast abscess                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cellulitis                               |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 6 / 2049 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchitis                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchopneumonia                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulitis                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 9 / 2062 (0.44%) | 8 / 2049 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium difficile colitis                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystitis  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device related infection                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 7 / 2062 (0.34%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |
| subjects affected / exposed                     | 8 / 2062 (0.39%) | 5 / 2049 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia sepsis                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder empyema                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gangrene  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 7 / 2049 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis Escherichia coli                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis norovirus                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Helicobacter infection                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incision site abscess                           |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lobar pneumonia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 4 / 2062 (0.19%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lymphangitis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mastitis  |                  |                  |  |
| subjects affected / exposed                     | 5 / 2062 (0.24%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nosocomial infection                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis media                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periorbital cellulitis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2062 (0.10%)  | 2 / 2049 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngeal abscess                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pilonidal cyst                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 29 / 2062 (1.41%) | 16 / 2049 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 30            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Pneumonia klebsiella                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia legionella                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%)  | 0 / 2049 (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 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Post procedural pneumonia                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%)  | 1 / 2049 (0.05%)  |  |
| 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                     | 2 / 2062 (0.10%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomembranous colitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomonas bronchitis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 2 / 2062 (0.10%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyometra  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory tract infection                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 8 / 2062 (0.39%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Skin infection                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue infection                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal infection                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Upper respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (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                     | 8 / 2062 (0.39%) | 7 / 2049 (0.34%) |  |
| occurrences causally related to treatment / all | 1 / 9            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Urosepsis                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2062 (0.15%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal infection                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular neuronitis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral diarrhoea                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulvitis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound infection                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 3 / 2049 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Decreased appetite                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 7 / 2049 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fluid overload                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercalcaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2062 (0.10%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 2 / 2049 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 4 / 2049 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypophagia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2062 (0.05%) | 1 / 2049 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obesity   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2062 (0.00%) | 1 / 2049 (0.05%) |  |
| 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                     | 1 / 2062 (0.05%) | 0 / 2049 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| 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>                     | Anastrozole          | Letrozole            |  |
|---|----------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                      |                      |  |
| subjects affected / exposed                           | 1762 / 2062 (85.45%) | 1747 / 2049 (85.26%) |  |
| Injury, poisoning and procedural complications        |                      |                      |  |
| Radiation skin injury                                 |                      |                      |  |
| subjects affected / exposed                           | 88 / 2062 (4.27%)    | 120 / 2049 (5.86%)   |  |
| occurrences (all)                                     | 88                   | 121                  |  |
| Vascular disorders                                    |                      |                      |  |
| Hot flush   |                      |                      |  |
| subjects affected / exposed                           | 666 / 2062 (32.30%)  | 666 / 2049 (32.50%)  |  |
| occurrences (all)                                     | 714                  | 702                  |  |
| Hypertension  |                      |                      |  |
| subjects affected / exposed                           | 145 / 2062 (7.03%)   | 152 / 2049 (7.42%)   |  |
| occurrences (all)                                     | 148                  | 152                  |  |
| Lymphoedema   |                      |                      |  |
| subjects affected / exposed                           | 177 / 2062 (8.58%)   | 158 / 2049 (7.71%)   |  |
| occurrences (all)                                     | 182                  | 165                  |  |
| Nervous system disorders                              |                      |                      |  |
| Dizziness   |                      |                      |  |
| subjects affected / exposed                           | 107 / 2062 (5.19%)   | 92 / 2049 (4.49%)    |  |
| occurrences (all)                                     | 116                  | 99                   |  |
| Headache  |                      |                      |  |
| subjects affected / exposed                           | 164 / 2062 (7.95%)   | 127 / 2049 (6.20%)   |  |
| occurrences (all)                                     | 184                  | 134                  |  |
| General disorders and administration                  |                      |                      |  |



|   |                        |                        |  |
|---|------------------------|------------------------|--|
| site conditions                                 |                        |                        |  |
| Fatigue   |                        |                        |  |
| subjects affected / exposed                     | 341 / 2062<br>(16.54%) | 345 / 2049<br>(16.84%) |  |
| occurrences (all)                               | 362                    | 368                    |  |
| Oedema peripheral                               |                        |                        |  |
| subjects affected / exposed                     | 104 / 2062 (5.04%)     | 100 / 2049 (4.88%)     |  |
| occurrences (all)                               | 109                    | 106                    |  |
| Gastrointestinal disorders                      |                        |                        |  |
| Nausea  |                        |                        |  |
| subjects affected / exposed                     | 148 / 2062 (7.18%)     | 127 / 2049 (6.20%)     |  |
| occurrences (all)                               | 162                    | 139                    |  |
| Respiratory, thoracic and mediastinal disorders |                        |                        |  |
| Cough   |                        |                        |  |
| subjects affected / exposed                     | 120 / 2062 (5.82%)     | 106 / 2049 (5.17%)     |  |
| occurrences (all)                               | 122                    | 115                    |  |
| Dyspnoea  |                        |                        |  |
| subjects affected / exposed                     | 92 / 2062 (4.46%)      | 111 / 2049 (5.42%)     |  |
| occurrences (all)                               | 94                     | 121                    |  |
| Skin and subcutaneous tissue disorders          |                        |                        |  |
| Alopecia  |                        |                        |  |
| subjects affected / exposed                     | 134 / 2062 (6.50%)     | 126 / 2049 (6.15%)     |  |
| occurrences (all)                               | 137                    | 131                    |  |
| Psychiatric disorders                           |                        |                        |  |
| Depression                                      |                        |                        |  |
| subjects affected / exposed                     | 129 / 2062 (6.26%)     | 141 / 2049 (6.88%)     |  |
| occurrences (all)                               | 133                    | 144                    |  |
| Insomnia  |                        |                        |  |
| subjects affected / exposed                     | 149 / 2062 (7.23%)     | 160 / 2049 (7.81%)     |  |
| occurrences (all)                               | 154                    | 165                    |  |
| Musculoskeletal and connective tissue disorders |                        |                        |  |
| Arthralgia                                      |                        |                        |  |
| subjects affected / exposed                     | 983 / 2062<br>(47.67%) | 983 / 2049<br>(47.97%) |  |
| occurrences (all)                               | 1192                   | 1181                   |  |
| Back pain                                       |                        |                        |  |
| subjects affected / exposed                     | 187 / 2062 (9.07%)     | 207 / 2049<br>(10.10%) |  |
| occurrences (all)                               | 199                    | 229                    |  |

|                                    |                     |                     |  |
|------------------------------------|---------------------|---------------------|--|
| Bone pain                          |                     |                     |  |
| subjects affected / exposed        | 120 / 2062 (5.82%)  | 138 / 2049 (6.73%)  |  |
| occurrences (all)                  | 127                 | 143                 |  |
| Musculoskeletal pain               |                     |                     |  |
| subjects affected / exposed        | 144 / 2062 (6.98%)  | 122 / 2049 (5.95%)  |  |
| occurrences (all)                  | 156                 | 129                 |  |
| Myalgia                            |                     |                     |  |
| subjects affected / exposed        | 211 / 2062 (10.23%) | 232 / 2049 (11.32%) |  |
| occurrences (all)                  | 223                 | 254                 |  |
| Osteopenia                         |                     |                     |  |
| subjects affected / exposed        | 172 / 2062 (8.34%)  | 202 / 2049 (9.86%)  |  |
| occurrences (all)                  | 172                 | 203                 |  |
| Osteoporosis                       |                     |                     |  |
| subjects affected / exposed        | 224 / 2062 (10.86%) | 221 / 2049 (10.79%) |  |
| occurrences (all)                  | 225                 | 223                 |  |
| Pain in extremity                  |                     |                     |  |
| subjects affected / exposed        | 174 / 2062 (8.44%)  | 167 / 2049 (8.15%)  |  |
| occurrences (all)                  | 193                 | 191                 |  |
| Metabolism and nutrition disorders |                     |                     |  |
| Hypercholesterolaemia              |                     |                     |  |
| subjects affected / exposed        | 151 / 2062 (7.32%)  | 155 / 2049 (7.56%)  |  |
| occurrences (all)                  | 151                 | 160                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 26 January 2006   | The protocol was updated to reflect the 2005 St Gallen's Early Breast Cancer consensus guidelines and the 2004 ASCO guidelines for the use of aromatase inhibitors for the adjuvant treatment of breast cancer and the use of bisphosphonates (Goldhirsch et al 2005, Winer et al Also, the steering committee recommended clear guidelines for different parties involved in the conduct of the trial including an independent group to control the analysis since the medication was not blinded.  |
| 19 September 2006 | The protocol was amended to incorporate participating investigators' feedback after enrolling their initial patients to the study. They suggested the protocol be consistent with its approach of using standard institutional practices rather than a mix of pre-specified examinations and standard care since there was extensive experience with both of these agents in terms of safety. Both agents received approval for this indication by multiple health authorities around the world. Also, the steering committee reconsidered the inclusion of patients who had received neo-adjuvant chemotherapy and revised the treatment guidelines for patients with hyperlipidemia. The secondary objectives were updated to include distant disease-free survival with appropriate statistical methodology added to include this in the statistical plan.  |
| 10 May 2007       | This amendment provided additional details concerning the central review of hormone receptors and HER2 status and added the central confirmation as a secondary objective for the study. Central confirmation of ER, PgR, and HER2 were mandatory for centers except where prohibited by regulations. Centers were asked to reconsent patients who had already been enrolled prior to the approval of amendment 3, if needed in order to ship their tumor blocks for central confirmation. Breast cancer researchers in general, strongly encouraged sites and patients to participate in studies which would further aid in the understanding and the complexity of this disease. The goal was to better understand which predictors defined the course of each breast cancer patient's disease. This was done by conducting correlative science studies. These studies were done in a subset of patients. Immunohistochemical analyses, tumor RNA profiling, tissue microarray analysis, estradiol, estrone and estrone sulfate levels, pharmacogenetics and proteomics comprised these studies. This amendment also updated the protocol information concerning statistical analysis of patients who had received neo-adjuvant therapy prior to study entry. The approval of amendment 2 allowed for the entry of these patients. New information regarding European Union regulatory guidelines and the lack of theoretical justification for the use of traditional statistical analyses in conjunction with a complex dynamic allocation became known after the approval of amendment 2. |

|                  |   |
|------------------|---|
| 25 March 2008    | Amendment 4 updated the procedures for the handling of the biological samples and the addition of an evaluation of disease status at Month 18. The steering committee added additional endocrine and proteomics sampling times to allow more flexibility for the sites and patients. Month 6, 18, or 24 were options. A maximum of two samples were required but when the samples were obtained was flexible. Since the exact timing of the pharmacogenetic sample was not critical, the steering committee broadened the time when the sample could be obtained. It could be obtained at either baseline, month 6, 12, 18, or 24. The secondary objectives were updated to remove breast cancer specific survival since the current data collection forms did not specifically collect this information. Without the specific information collected, this endpoint could not be determined. Also, eliminated was the need to stratify by presence or absence of neo-adjuvant chemotherapy in the statistical analysis plan. Neo-adjuvant chemotherapy was not a stratification factor for the determination of the treatment assignment. There were very few patients in this category so this was of minimal interest. The formal process for handling protocol violations was added to the Procedures section of the protocol. Amendment 4 called for the completion of the study at 959 disease free survival (DFS) events and 5 years after the completion of enrollment. The event rate was lower than initially planned in the protocol, and the protocol was amended to extend the follow up period in order to continue the collection of the primary endpoint data. The study's second interim analysis was conducted after the data cutoff of 21-Nov-2013. It was based on 704 DFS events. |
| 19 December 2013 | Amendment 5 was created to extend the follow up period to continue to collect events/endpoints. Amendment 5 was released to the countries and sites in January 2014. It was approved by several of the countries, but none of the patients were re-consented. Based on the Kaplan-Meier curve from the second interim analysis, the statistical team modeled that it would take until 2022 to reach the 959 DFS events, the trial's primary endpoint. Considering that only approximately 1000 patients globally would be available for re-consenting and follow-up, the decision was made not to implement protocol amendment 5, which extended the follow-up period, and therefore terminate the trial early. Amendment 5 had been released, submitted, and approved in several countries and the global and local processes for early termination of the trial were implemented. No patients were re-consented nor were active participants in the extended follow-up period as part of Amendment 5.   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Notes: