



## Clinical trial results: Strategic Timing of AntiRetroviral Treatment(START) Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2008-006439-12                            |
| Trial protocol           | BE FI ES DE GB GR IT SE PT IE EE NO AT CZ |
| Global end of trial date | 27 July 2022                              |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 23 October 2023 |
| First version publication date | 23 October 2023 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | INSIGHT001:START |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00867048 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Regents of the University of Minnesota  |
| Sponsor organisation address | Office of the Vice President for Research, 420 Johnston Hall,<br>101 Pleasant St. SE, Minneapolis, United States, 55455 |
| Public contact               | Jens Lundgren, CHIP - Rigshospitalet, University of<br>Copenhagen, 45 3545 5757, jens.lundgren@regionh.dk               |
| Scientific contact           | Jens Lundgren, CHIP - Rigshospitalet, University of<br>Copenhagen, 45 3545 5757, jens.lundgren@regionh.dk               |

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                       | 30 June 2023 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 27 July 2022 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 27 July 2022 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of START was to determine whether starting ART early (at CD4 > 500) is superior to deferring ART until indicated by (then-current) guidelines at delaying the occurrence of a composite outcome consisting of AIDS, non-AIDS, or death from any cause.

Based on two scientific hypotheses, both which take advantage of the randomized design of START and the extended follow-up through 2021, the primary objective of the extended follow-up period was to determine whether the benefit of early ART as compared to deferred ART in delaying the occurrence of a composite outcome consisting of AIDS, non-AIDS, or death from any cause is maintained, increased or reduced.

Protection of trial subjects:

Participants were in regular contact with the study site, as this was where they were getting their primary care for HIV infection. Any side effects or necessary changes in medication could be identified promptly.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 15 April 2009 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Morocco: 43     |
| Country: Number of subjects enrolled | Uganda: 348     |
| Country: Number of subjects enrolled | Denmark: 33     |
| Country: Number of subjects enrolled | Luxembourg: 5   |
| Country: Number of subjects enrolled | Switzerland: 31 |
| Country: Number of subjects enrolled | Argentina: 216  |
| Country: Number of subjects enrolled | Australia: 109  |
| Country: Number of subjects enrolled | Chile: 76       |
| Country: Number of subjects enrolled | India: 91       |
| Country: Number of subjects enrolled | Israel: 28      |
| Country: Number of subjects enrolled | Malaysia: 18    |
| Country: Number of subjects enrolled | Mexico: 48      |
| Country: Number of subjects enrolled | Nigeria: 49     |
| Country: Number of subjects enrolled | Thailand: 247   |
| Country: Number of subjects enrolled | Brazil: 619     |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Mali: 41            |
| Country: Number of subjects enrolled | Peru: 215           |
| Country: Number of subjects enrolled | United States: 507  |
| Country: Number of subjects enrolled | South Africa: 518   |
| Country: Number of subjects enrolled | Norway: 15          |
| Country: Number of subjects enrolled | Poland: 68          |
| Country: Number of subjects enrolled | Portugal: 67        |
| Country: Number of subjects enrolled | Spain: 234          |
| Country: Number of subjects enrolled | Sweden: 2           |
| Country: Number of subjects enrolled | United Kingdom: 339 |
| Country: Number of subjects enrolled | Austria: 7          |
| Country: Number of subjects enrolled | Belgium: 102        |
| Country: Number of subjects enrolled | Czechia: 13         |
| Country: Number of subjects enrolled | Estonia: 8          |
| Country: Number of subjects enrolled | Finland: 23         |
| Country: Number of subjects enrolled | France: 111         |
| Country: Number of subjects enrolled | Germany: 312        |
| Country: Number of subjects enrolled | Greece: 101         |
| Country: Number of subjects enrolled | Ireland: 7          |
| Country: Number of subjects enrolled | Italy: 33           |
| Worldwide total number of subjects   | 4684                |
| EEA total number of subjects         | 1141                |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| 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)                      | 4653 |
| From 65 to 84 years                       | 31   |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Adults with documented HIV infection and a current CD4+ cell count > 500 cells/mm<sup>3</sup> who have never received antiretroviral treatment

### Period 1

|                              |                               |
|------------------------------|-------------------------------|
| Period 1 title               | Entire trial (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>             | Immediate antiretroviral therapy |

Arm description:

Antiretroviral-naïve participants with HIV infection and CD4+ > 500 cell/mm<sup>3</sup> will begin antiretroviral treatment immediately following randomization with regimen of any approved drugs, as determined by their treating clinician

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Antiretroviral therapy |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Tablet        |
| Routes of administration               | Oral use               |

Dosage and administration details:

For each participant, the clinician constructed a first-line antiretroviral regimen per current treatment guidelines from drugs approved for use in that country.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Deferred antiretroviral therapy |
|------------------|---------------------------------|

Arm description:

Participants with HIV infection and CD4 > 500 cell/mm<sup>3</sup> deferred ART initiation until their CD4 dropped to < 350 cell/mm<sup>3</sup> or an AIDS-related condition developed.

|  |                        |
|--|------------------------|
| Arm type                               | Standard of care       |
| Investigational medicinal product name | Antiretroviral therapy |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet, Capsule        |
| Routes of administration               | Oral use               |

Dosage and administration details:

For each participant, the clinician constructed a first-line antiretroviral regimen per current treatment guidelines from drugs approved for use in that country.

| <b>Number of subjects in period 1</b> | Immediate<br>antiretroviral<br>therapy | Deferred<br>antiretroviral<br>therapy |
|---------------------------------------|--|---------------------------------------|
| Started                               | 2325                                   | 2359                                  |
| Completed                             | 2325                                   | 2359                                  |

## Baseline characteristics

### Reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | Immediate antiretroviral therapy |
| Reporting group description:   |                                  |
| Antiretroviral-naïve participants with HIV infection and CD4+ > 500 cell/mm <sup>3</sup> will begin antiretroviral treatment immediately following randomization with regimen of any approved drugs, as determined by their treating clinician |                                  |
| Reporting group title  | Deferred antiretroviral therapy  |
| Reporting group description:   |                                  |
| Participants with HIV infection and CD4 > 500 cell/mm <sup>3</sup> deferred ART initiation until their CD4 dropped to < 350 cell/mm <sup>3</sup> or an AIDS-related condition developed.   |                                  |

| Reporting group values                             | Immediate antiretroviral therapy | Deferred antiretroviral therapy | Total |
|--|----------------------------------|---------------------------------|-------|
| Number of subjects                                 | 2325                             | 2359                            | 4684  |
| Age categorical                                    |                                  |                                 |       |
| Units: Subjects                                    |                                  |                                 |       |
| In utero   | 0                                | 0                               | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                                | 0                               | 0     |
| Newborns (0-27 days)                               | 0                                | 0                               | 0     |
| Infants and toddlers (28 days-23 months)           | 0                                | 0                               | 0     |
| Children (2-11 years)                              | 0                                | 0                               | 0     |
| Adolescents (12-17 years)                          | 0                                | 0                               | 0     |
| Adults (18-64 years)                               | 2308                             | 2345                            | 4653  |
| From 65-84 years                                   | 17                               | 14                              | 31    |
| 85 years and over                                  | 0                                | 0                               | 0     |
| Age continuous                                     |                                  |                                 |       |
| Units: years                                       |                                  |                                 |       |
| arithmetic mean                                    | 36.8                             | 36.8                            |       |
| standard deviation                                 | ± 10.2                           | ± 10.1                          | -     |
| Gender categorical                                 |                                  |                                 |       |
| Units: Subjects                                    |                                  |                                 |       |
| Female   | 624                              | 633                             | 1257  |
| Male   | 1701                             | 1726                            | 3427  |

### Subject analysis sets

|   |  |
|---|--|
| Subject analysis set title  | All participants with documented HIV infection |
| Subject analysis set type   | Full analysis                                  |
| Subject analysis set description:   |  |
| Among the 4688 putatively HIV-infected participants enrolled, 4 were ultimately found to be not infected with HIV. These 4 participants are not included in outcome analyses. |  |

| Reporting group values | All participants with documented HIV infection |  |  |
|------------------------|--|--|--|
| Number of subjects     | 4684   |  |  |

|   |        |  |  |
|---|--------|--|--|
| Age categorical                                       |        |  |  |
| Units: Subjects                                       |        |  |  |
| In utero  | 0      |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0      |  |  |
| Newborns (0-27 days)                                  | 0      |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0      |  |  |
| Children (2-11 years)                                 | 0      |  |  |
| Adolescents (12-17 years)                             | 0      |  |  |
| Adults (18-64 years)                                  | 4653   |  |  |
| From 65-84 years                                      | 31     |  |  |
| 85 years and over                                     | 0      |  |  |
| Age continuous  |        |  |  |
| Units: years  |        |  |  |
| arithmetic mean                                       | 36.8   |  |  |
| standard deviation                                    | ± 10.2 |  |  |
| Gender categorical                                    |        |  |  |
| Units: Subjects                                       |        |  |  |
| Female  | 1257   |  |  |
| Male  | 3427   |  |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Immediate antiretroviral therapy               |
| Reporting group description:<br>Antiretroviral-naïve participants with HIV infection and CD4+ > 500 cell/mm <sup>3</sup> will begin antiretroviral treatment immediately following randomization with regimen of any approved drugs, as determined by their treating clinician |  |
| Reporting group title  | Deferred antiretroviral therapy                |
| Reporting group description:<br>Participants with HIV infection and CD4 > 500 cell/mm <sup>3</sup> deferred ART initiation until their CD4 dropped to < 350 cell/mm <sup>3</sup> or an AIDS-related condition developed.   |  |
| Subject analysis set title   | All participants with documented HIV infection |
| Subject analysis set type  | Full analysis                                  |
| Subject analysis set description:<br>Among the 4688 putatively HIV-infected participants enrolled, 4 were ultimately found to be not infected with HIV. These 4 participants are not included in outcome analyses.   |  |

### Primary: Composite primary outcome

|   |                           |
|---|---------------------------|
| End point title   | Composite primary outcome |
| End point description:<br>Composite endpoint of an AIDS event, serious non-AIDS event (cardiovascular disease, non-AIDS cancer, end-stage renal disease, decompensated liver disease), or death from any cause. |                           |
| End point type  | Primary                   |
| End point timeframe:<br>Randomization through 31 December 2021  |                           |

| End point values            | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |  |
|-----------------------------|----------------------------------|---------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                 |  |  |
| Number of subjects analysed | 2325                             | 2359                            |  |  |
| Units: participants         | 133                              | 215                             |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Composite primary outcome  |
| Statistical analysis description:<br>Cox regression, time to first event. Hazard ratio Immediate/Deferred (95% confidence interval); pvalue; alpha=0.05; 2-sided. Model stratified by geographic region. |  |
| Comparison groups  | Immediate antiretroviral therapy v Deferred antiretroviral therapy |



|   |                                     |
|---|-------------------------------------|
| Number of subjects included in analysis | 4684                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001                             |
| Method                                  | Cox proportional hazards regression |
| Parameter estimate                      | Hazard ratio (HR)                   |
| Point estimate                          | 0.61                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.49                                |
| upper limit                             | 0.76                                |

### Secondary: AIDS or AIDS-related death

|   |                            |
|---|----------------------------|
| End point title   | AIDS or AIDS-related death |
| End point description:  |                            |
| A component of the composite primary endpoint. Time to first event: AIDS event or death from AIDS-related event |                            |
| End point type  | Secondary                  |
| End point timeframe:  |                            |
| Randomization through 31 December 2021  |                            |

| End point values            | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |  |
|-----------------------------|----------------------------------|---------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                 |  |  |
| Number of subjects analysed | 2325                             | 2359                            |  |  |
| Units: participants         | 31                               | 83                              |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | AIDS   |
| Comparison groups                       | Immediate antiretroviral therapy v Deferred antiretroviral therapy |
| Number of subjects included in analysis | 4684   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.001  |
| Method                                  | Cox proportional hazards regression                                |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.37   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.25    |
| upper limit         | 0.56    |

## Secondary: Serious non-AIDS

|  |                  |
|--|------------------|
| End point title  | Serious non-AIDS |
| End point description:   |                  |
| A component of the composite primary outcome. Time to first event: cardiovascular disease, end-stage renal disease, decompensated liver diseases, non-AIDS-associated cancer, death from causes other than AIDS. |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| Randomization through 31 December 2021   |                  |

| End point values            | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |  |
|-----------------------------|----------------------------------|---------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                 |  |  |
| Number of subjects analysed | 2325                             | 2359                            |  |  |
| Units: participants         | 107                              | 137                             |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Serious non-AIDS   |
| Comparison groups                       | Immediate antiretroviral therapy v Deferred antiretroviral therapy |
| Number of subjects included in analysis | 4684   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.053  |
| Method                                  | Cox proportional hazards regression                                |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.78   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.61   |
| upper limit                             | 1  |

## Secondary: All-cause mortality

|                 |                     |
|-----------------|---------------------|
| End point title | All-cause mortality |
|-----------------|---------------------|

End point description:

A component of the primary composite outcome. Time-to-event analysis.

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

End point timeframe:

Randomization through 31 December 2021

| End point values            | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |  |
|-----------------------------|----------------------------------|---------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group                 |  |  |
| Number of subjects analysed | 2325                             | 2359                            |  |  |
| Units: participants         | 66                               | 85                              |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | All-cause mortality  |
| Comparison groups                       | Immediate antiretroviral therapy v Deferred antiretroviral therapy |
| Number of subjects included in analysis | 4684   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.13   |
| Method                                  | Cox proportional hazards regression                                |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.78   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.57   |
| upper limit                             | 1.08   |

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Randomization through 31 December 2017 for serious adverse events; deaths are reported through 31 December 2021.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Immediate antiretroviral therapy |
|-----------------------|----------------------------------|

Reporting group description:

Participants with HIV infection and CD4+ > 500 cell/mm<sup>3</sup> will begin antiretroviral treatment with regimen of any approved drugs, as determined by their treating clinician.

Non-serious events were not reported in this trial.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Deferred antiretroviral therapy |
|-----------------------|---------------------------------|

Reporting group description:

Participants with HIV infection and CD4 > 500 cells/mm<sup>3</sup> waited until they met global treatment guidelines to begin antiretroviral therapy (i.e., until CD4 cell count dropped below 350 cell/mm<sup>3</sup> or an AIDS-related condition developed).

Non-serious events were not reported in this trial.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events were collected in START. As a strategy trial, all medications being used were approved and being used within indication.

| Serious adverse events  | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |
|---|----------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events                   |                                  |                                 |  |
| subjects affected / exposed   | 430 / 2325 (18.49%)              | 498 / 2359 (21.11%)             |  |
| number of deaths (all causes)                                       | 66                               | 85                              |  |
| number of deaths resulting from adverse events                      |                                  |                                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                                 |  |
| Adenocarcinoma gastric  |                                  |                                 |  |
| subjects affected / exposed   | 1 / 2325 (0.04%)                 | 0 / 2359 (0.00%)                |  |
| occurrences causally related to treatment / all                     | 0 / 1                            | 0 / 0                           |  |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                           |  |
| Adrenal adenoma   |                                  |                                 |  |
| subjects affected / exposed   | 1 / 2325 (0.04%)                 | 0 / 2359 (0.00%)                |  |
| occurrences causally related to treatment / all                     | 0 / 1                            | 0 / 0                           |  |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                           |  |
| Anal cancer   |                                  |                                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal squamous cell carcinoma                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign hydatidiform mole                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Burkitt's lymphoma                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cancer pain                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Castleman's disease                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervix carcinoma                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Clear cell renal cell carcinoma                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extragenital primary seminoma (pure)            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrosarcoma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung adenocarcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung cancer metastatic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Meningioma benign                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastasis                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic malignant melanoma                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myeloid leukaemia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Neurilemmoma benign                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroma   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-small cell lung cancer metastatic           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Papillary thyroid cancer                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal cancer                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                             | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Seminoma  |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Small cell lung cancer                                  |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Small cell lung cancer metastatic                       |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 1            |  |
| Squamous cell carcinoma of lung                         |                  |                  |  |
| subjects affected / exposed                             | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all              | 0 / 1            | 0 / 0            |  |
| Testicular germ cell cancer                             |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Testis cancer   |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Transitional cell cancer of the renal pelvis and ureter |                  |                  |  |
| subjects affected / exposed                             | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all         | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all              | 0 / 0            | 0 / 0            |  |
| Transitional cell carcinoma metastatic                  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Uterine leiomyoma                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal carcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Aortic aneurysm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortitis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 5 / 2325 (0.22%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hypertensive crisis                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (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                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vena cava thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Appendicectomy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pregnancy, puerperium and perinatal conditions  |                  |                  |  |
| Abortion incomplete                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion spontaneous                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion threatened                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Cephalo-pelvic disproportion<br>subjects affected / exposed | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1            | 0 / 0            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Ectopic pregnancy<br>subjects affected / exposed            | 4 / 2325 (0.17%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 5            | 0 / 2            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Foetal death<br>subjects affected / exposed                 | 2 / 2325 (0.09%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 2            | 1 / 3            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Foetal distress syndrome<br>subjects affected / exposed     | 4 / 2325 (0.17%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 4            | 0 / 5            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Gestational hypertension<br>subjects affected / exposed     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1            | 1 / 2            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Haemorrhage in pregnancy<br>subjects affected / exposed     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0            | 0 / 1            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Oligohydramnios<br>subjects affected / exposed              | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1            | 0 / 0            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Pre-eclampsia<br>subjects affected / exposed                | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1            | 0 / 0            |  |
| deaths causally related to<br>treatment / all               | 0 / 0            | 0 / 0            |  |
| Premature delivery  |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Premature labour                                     |                  |                  |  |
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Premature rupture of membranes                       |                  |                  |  |
| subjects affected / exposed                          | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Prolonged labour                                     |                  |                  |  |
| subjects affected / exposed                          | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Ruptured ectopic pregnancy                           |                  |                  |  |
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Umbilical cord prolapse                              |                  |                  |  |
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Chest pain   |                  |                  |  |
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Chills   |                  |                  |  |
| subjects affected / exposed                          | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Complication of device insertion                     |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Death   |                  |                   |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 12 / 2359 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 12            |  |
| Drowning  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2             |  |
| Drug withdrawal syndrome                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fatigue   |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gait disturbance                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Influenza like illness                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Impaired self-care                              |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Multiple organ dysfunction syndrome             |                  |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Necrobiosis                                     |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Non-cardiac chest pain                          |                  |                   |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Peripheral swelling                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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 / 2325 (0.34%) | 11 / 2359 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Strangulated hernia                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Systemic inflammatory response syndrome         |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Abscess neck                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Acute hepatitis B                               |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Hypersensitivity                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaphylactic shock                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| 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 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sarcoidosis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Social circumstances                            |                  |                  |  |
| Homicide  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Substance use                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Abnormal uterine bleeding                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cystocele                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital rash                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intermenstrual bleeding                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Priapism  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Testicular pain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Testicular torsion                              |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine adhesions                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aspiration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Asthma  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cough   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspnoea  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive airways disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleurisy  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory failure                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Restrictive pulmonary disease                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillar hypertrophy                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheomalacia                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Acute psychosis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute stress disorder                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Affective disorder                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Agitation                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol abuse                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol withdrawal syndrome                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcoholism                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anxiety   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar I disorder                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar disorder                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Burnout syndrome                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiovascular somatic symptom disorder         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Completed suicide                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 1 / 5            |  |
| Conversion disorder                             |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Delirium  |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Depression                                      |                  |                   |  |
| subjects affected / exposed                     | 8 / 2325 (0.34%) | 13 / 2359 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 9            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Depression suicidal                             |                  |                   |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Drug abuse                                      |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Drug dependence                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hallucination                                   |                  |                   |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hallucination, auditory                         |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Homicidal ideation                              |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intentional self-injury                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Major depression                                |                  |                  |  |
| subjects affected / exposed                     | 7 / 2325 (0.30%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 2 / 8            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Panic attack                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Persecutory delusion                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric decompensation                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychotic disorder                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizoaffective disorder                        |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Schizophrenia                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Self-injurious ideation                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Substance abuse                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 3 / 2359 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Substance-induced mood disorder                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Substance-induced psychotic disorder            |                   |                   |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%)  | 3 / 2359 (0.13%)  |  |
| occurrences causally related to treatment / all | 3 / 6             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Suicidal ideation                               |                   |                   |  |
| subjects affected / exposed                     | 14 / 2325 (0.60%) | 16 / 2359 (0.68%) |  |
| occurrences causally related to treatment / all | 9 / 22            | 3 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Suicide attempt                                 |                   |                   |  |
| subjects affected / exposed                     | 24 / 2325 (1.03%) | 20 / 2359 (0.85%) |  |
| occurrences causally related to treatment / all | 9 / 34            | 4 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hepatobiliary disorders                         |                   |                   |  |
| Autoimmune hepatitis                            |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary colic                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cholecystitis chronic                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholelithiasis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholelithiasis migration                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug-induced liver injury                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic failure                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Hepatitis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis acute                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Hyperbilirubinaemia                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 4 / 4            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Blood glucose increased                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| 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  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Abdominal injury                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Accidental overdose                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Accidental poisoning                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol poisoning                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbon monoxide poisoning                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Clavicle fracture                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Contusion                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Craniocerebral injury                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Extradural haematoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye injury                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fall  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibula fracture                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Forearm fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foreign body in gastrointestinal tract          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture of penis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal procedural complication        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal stoma complication             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gun shot wound                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Hand fracture                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intentional overdose                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament injury                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb traumatic amputation                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple fractures                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple injuries                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Nasal injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax traumatic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post concussion syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post lumbar puncture syndrome                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematoma                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematuria                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post-traumatic neck syndrome                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural complication                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reactive gastropathy                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Scrotal haematoma                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin laceration                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue injury                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord injury cervical                     |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stab wound                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon injury                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| 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                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Testicular injury                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Tibia fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic haematoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic haemothorax                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic intracranial haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft thrombosis                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound dehiscence                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (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                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Alagille syndrome                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anencephaly                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital hydrocephalus                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital hydronephrosis                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Microcephaly                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patent ductus arteriosus                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheo-oesophageal fistula                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular septal defect                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute myocardial infarction                     |                  |                  |  |
| subjects affected / exposed                     | 8 / 2325 (0.34%) | 6 / 2359 (0.25%) |  |
| occurrences causally related to treatment / all | 3 / 8            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina pectoris                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina unstable                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic valve stenosis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arrhythmia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Arteriosclerosis coronary artery                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial fibrillation                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial flutter                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure acute                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac failure congestive                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiomyopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery disease                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foetal arrhythmia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mitral valve incompetence                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myocardial infarction                           |                  |                  |  |
| subjects affected / exposed                     | 5 / 2325 (0.22%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Palpitations                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Silent myocardial infarction                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus tachycardia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subvalvular aortic stenosis                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Aphasia   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arachnoid cyst                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bell's palsy                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cauda equina syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Central nervous system lesion                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cerebrovascular accident                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cognitive disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Demyelination                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug withdrawal convulsions                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial paresis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Generalised tonic-clonic seizure                |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Guillain-Barre syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| 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                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhagic transformation stroke              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Hydrocephalus                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Idiopathic intracranial hypertension            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intracranial mass                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic encephalopathy                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuropathy peripheral                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraesthesia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial seizures                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Petit mal epilepsy                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyneuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postictal state                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord compression                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vlith nerve paralysis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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                     | 5 / 2325 (0.22%) | 7 / 2359 (0.30%) |  |
| occurrences causally related to treatment / all | 1 / 6            | 4 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile bone marrow aplasia                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Normochromic normocytic anaemia                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Tinnitus  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo positional                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Opsoclonus myoclonus                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal artery occlusion                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Disorder of orbit                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vision blurred                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain lower                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal strangulated hernia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute abdomen                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcoholic pancreatitis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fissure                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal haemorrhage                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal pruritus                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anogenital dysplasia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ulcerative                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer perforation                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysphagia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faecaloma                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Food poisoning                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Functional gastrointestinal disorder            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric disorder                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal toxicity                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoidal haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids thrombosed                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus   |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| 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                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia, obstructive                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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                     | 4 / 2325 (0.17%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Intra-abdominal fluid collection                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine perforation                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mallory-Weiss syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Megacolon                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstruction gastric                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Odynophagia                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal achalasia                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal rupture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Proctitis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 5 / 2359 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal perforation                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retroperitoneal haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Strangulated umbilical hernia                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth impacted                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Dermal cyst                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug eruption                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erythema multiforme                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Panniculitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin lesion                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin necrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxic skin eruption                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Xanthoma  |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Renal and urinary disorders                     |                   |                  |  |
| Acute kidney injury                             |                   |                  |  |
| subjects affected / exposed                     | 11 / 2325 (0.47%) | 6 / 2359 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Anuria  |                   |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Calculus urinary                                |                   |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Diabetic nephropathy                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| End stage renal disease                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Glomerulonephritis                              |                   |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Nephrolithiasis                                 |                   |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%)  | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Nephropathy                                     |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureterolithiasis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary bladder haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract obstruction                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis reactive                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bursitis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture nonunion                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar spinal stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal chest pain                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteoarthritis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteonecrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain in extremity                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyarthrititis                                 |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhabdomyolysis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Abscess   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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                     | 7 / 2325 (0.30%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute hepatitis C                               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 4 / 2325 (0.17%)  | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anal abscess                                    |                   |                   |  |
| subjects affected / exposed                     | 5 / 2325 (0.22%)  | 13 / 2359 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendicitis                                    |                   |                   |  |
| subjects affected / exposed                     | 24 / 2325 (1.03%) | 17 / 2359 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendicitis perforated                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arteriovenous graft site abscess                |                   |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthritis bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacteraemia                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%)  | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacterial diarrhoea                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%)  | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacterial pyelonephritis                        |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bronchitis                                      |                  |                   |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bronchitis viral                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Burn infection                                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Campylobacter gastroenteritis                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Campylobacter sepsis                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Catheter site infection                         |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cellulitis                                      |                  |                   |  |
| subjects affected / exposed                     | 5 / 2325 (0.22%) | 10 / 2359 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cellulitis staphylococcal                       |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Complicated appendicitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cryptosporidiosis infection                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dengue fever                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dengue haemorrhagic fever                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device related infection                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot infection                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea infectious                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis intestinal haemorrhagic          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysentery                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Embolic pneumonia                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis bacterial                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epididymitis                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiglottic abscess                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 4 / 2359 (0.17%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Escherichia pyelonephritis                      |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Escherichia urinary tract infection             |                  |                   |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Extradural abscess                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Febrile infection                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fournier's gangrene                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Furuncle  |                  |                   |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastroenteritis                                 |                  |                   |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 10 / 2359 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastroenteritis Escherichia coli                |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis bacterial                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis cryptosporidial                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis salmonella                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis shigella                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis viral                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal infection                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital herpes simplex                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Giardiasis                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gonorrhoea                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Groin abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HIV associated nephropathy                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HIV peripheral neuropathy                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis A                                     |                  |                  |  |
| subjects affected / exposed                     | 6 / 2325 (0.26%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis C                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes simplex necrotising retinopathy          |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 7 / 2359 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral discitis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine infection                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymph node abscess                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphogranuloma venereum                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malaria   |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 9 / 2359 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis streptococcal                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis viral                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningoencephalitis herpetic                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mononucleosis syndrome                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mycobacterium abscessus infection               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrotising fasciitis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurosyphilis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 6 / 2359 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenic sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ophthalmic herpes zoster                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound sepsis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orchitis  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis chronic                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis media acute                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paronychia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parotid abscess                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parotitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic inflammatory disease                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Perirectal abscess                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonsillar abscess                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pertussis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngotonsillitis                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pilonidal disease                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumococcal bacteraemia                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Pneumonia aspiration                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Proctitis chlamydial                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 2325 (0.17%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 2325 (0.13%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyomyositis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal abscess                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rubella   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Scrotal abscess                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Secondary syphilis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 6 / 2359 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Sepsis syndrome                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Shigella infection                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft tissue infection                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal abscess                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal skin infection                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal bacteraemia                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal sepsis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Strongyloidiasis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous abscess                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syphilis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 4 / 2359 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tertiary syphilis                               |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillitis streptococcal                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tuberculosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Tubo-ovarian abscess                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Typhoid fever                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 2325 (0.22%) | 3 / 2359 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urosepsis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varicella                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral infection                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral pharyngitis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral upper respiratory tract infection         |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (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                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound infection staphylococcal                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Abnormal loss of weight                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus inadequate control            |                  |                  |  |
| subjects affected / exposed                     | 2 / 2325 (0.09%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidosis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 2 / 2359 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic metabolic decompensation               |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gout  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 2325 (0.04%) | 0 / 2359 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 2325 (0.00%) | 1 / 2359 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

Frequency threshold for reporting non-serious adverse events: 0.1 %

| <b>Non-serious adverse events</b>                     | Immediate antiretroviral therapy | Deferred antiretroviral therapy |  |
|---|----------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events |                                  |                                 |  |
| subjects affected / exposed                           | 0 / 2325 (0.00%)                 | 0 / 2359 (0.00%)                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 25 October 2010  | Removed "consecutive" from CD4 eligibility criterion (2 CD4+ cell counts > 500 cells/mL)<br>Clarified exclusion criteria 3 and 7 to specify that these were as assessed at randomization and before randomization respectively.<br>Incorporated language regarding appropriate clinical management for participants in the deferred group whose CD4+ cell count is declining.<br>Sample size section modified after performing the planned sample size re-estimation.  |
| 01 February 2016 | The Data Safety Monitoring Board (DSMB) unblinded the trial on 26 May 2015. At a planned review the DSMB informed the trial leadership and sponsor that an interim monitoring boundary for efficacy had been crossed and recommended all participants begin antiretroviral therapy and continue follow-up. This protocol version described follow-up through 2021.<br>Study objectives were revised and expanded, but the primary endpoint remains the same.<br>Data collection reduced.<br>Antiretroviral therapy will continue to be provided through the study through 2017 only; alternate arrangements for therapy must be made before that time. |
| 28 August 2017   | Further reduced data collection to one time point/year, to be collected primarily by abstraction from medical records of participants' regular care.<br>Serious events no longer reported on a real-time basis or forwarded to regulators by the sponsor. Unscheduled hospitalizations will continue to be reported as part of the annual data collection.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26192873>

<http://www.ncbi.nlm.nih.gov/pubmed/37213438>