



## Clinical trial results:

### A Clinical Outcomes Study to Evaluate the Effects of IL-6 Receptor Blockade With Tocilizumab (TCZ) in Comparison With Etanercept (ETA) on the Rate of Cardiovascular Events in Patients With Moderate to Severe Rheumatoid Arthritis (RA)

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2010-020065-24                      |
| Trial protocol           | GB HU LV BE AT LT CZ DE ES NL GR IT |
| Global end of trial date | 25 March 2016                       |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 June 2017 |
| First version publication date | 29 June 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WA25204 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hoffmann-La Roche  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel,, Switzerland,                          |
| Public contact               | Medical Communications, Hoffmann-La Roche,<br>genentech@druginfo.com |
| Scientific contact           | Medical Communications, Hoffmann-La Roche,<br>genentech@druginfo.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 25 March 2016 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 25 March 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 25 March 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare prospectively in patients treated with TCZ or ETA, the time to first occurrence of any component of the composite of:

- Cardiovascular (CV) death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke of all classifications (ischemic, hemorrhagic, or undetermined origin)

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. Approval from the Independent Ethics Committee/Institutional Review Board was obtained before study start and was documented in a letter to the Investigator specifying the date on which the committee met and granted the approval.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 02 August 2011 |
| 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 | Argentina: 313             |
| Country: Number of subjects enrolled | Austria: 10                |
| Country: Number of subjects enrolled | Belgium: 15                |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 58 |
| Country: Number of subjects enrolled | Canada: 79                 |
| Country: Number of subjects enrolled | Chile: 124                 |
| Country: Number of subjects enrolled | Czech Republic: 206        |
| Country: Number of subjects enrolled | Germany: 65                |
| Country: Number of subjects enrolled | Ecuador: 40                |
| Country: Number of subjects enrolled | Spain: 88                  |
| Country: Number of subjects enrolled | France: 11                 |
| Country: Number of subjects enrolled | United Kingdom: 62         |
| Country: Number of subjects enrolled | Greece: 14                 |
| Country: Number of subjects enrolled | Croatia: 40                |
| Country: Number of subjects enrolled | Hungary: 54                |
| Country: Number of subjects enrolled | India: 31                  |
| Country: Number of subjects enrolled | Italy: 18                  |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Lithuania: 38           |
| Country: Number of subjects enrolled | Latvia: 41              |
| Country: Number of subjects enrolled | Mexico: 335             |
| Country: Number of subjects enrolled | Malaysia: 18            |
| Country: Number of subjects enrolled | Netherlands: 4          |
| Country: Number of subjects enrolled | Philippines: 21         |
| Country: Number of subjects enrolled | Poland: 215             |
| Country: Number of subjects enrolled | Romania: 149            |
| Country: Number of subjects enrolled | Russian Federation: 206 |
| Country: Number of subjects enrolled | Serbia: 64              |
| Country: Number of subjects enrolled | Turkey: 10              |
| Country: Number of subjects enrolled | United States: 671      |
| Country: Number of subjects enrolled | South Africa: 59        |
| Country: Number of subjects enrolled | Israel: 21              |
| Worldwide total number of subjects   | 3080                    |
| EEA total number of subjects         | 1030                    |

Notes:

### Subjects enrolled per age group

|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 2182 |
| From 65 to 84 years                       | 895  |
| 85 years and over                         | 3    |

## Subject disposition

### Recruitment

Recruitment details:

A total of 3080 patients were enrolled from 353 sites, across 31 countries

### Pre-assignment

Screening details:

The target population was patients with moderate to severe rheumatoid arthritis  $\geq 6$  months duration and for whom non-biologic DMARD treatment or treatment with an anti-tumor necrosis factor (anti-TNF) agent was inadequate.

Patients were required to be 50 years or older and to have at least one additional CV risk factor beyond RA.

### Period 1

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

### Arms

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

Arm description:

Participants received 8 mg/kg tocilizumab IV every 4 weeks until switch to another RA therapy or up to 4.9 years.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Tocilizumab   |
| Investigational medicinal product code |   |
| Other name                             | RoActemra, Actemra, RO4877533                         |
| Pharmaceutical forms                   | Solution for injection/infusion in pre-filled syringe |
| Routes of administration               | Intravenous use                                       |

Dosage and administration details:

Tocilizumab was administered at a dose of 8 mg/kg every 4 weeks.

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

Arm description:

Participants received 50 mg etanercept subcutaneously weekly until switch to another RA therapy or up to 4.9 years.

|  |   |
|--|---|
| Arm type                               | Active comparator                                     |
| Investigational medicinal product name | Etanercept  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for injection/infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                                      |

Dosage and administration details:

Participants received 50 mg etanercept subcutaneously weekly

| <b>Number of subjects in period 1</b> | Tocilizumab | Etanercept |
|---------------------------------------|-------------|------------|
| Started                               | 1538        | 1542       |
| Completed                             | 1482        | 1475       |
| Not completed                         | 56          | 67         |
| Adverse event, serious fatal          | 30          | 34         |
| Consent withdrawn by subject          | 13          | 16         |
| Info not recorded                     | 10          | 16         |
| Lost to follow-up                     | 3           | 1          |

## Baseline characteristics

### Reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Tocilizumab |
| Reporting group description:  |             |
| Participants received 8 mg/kg tocilizumab IV every 4 weeks until switch to another RA therapy or up to 4.9 years.   |             |
| Reporting group title   | Etanercept  |
| Reporting group description:  |             |
| Participants received 50 mg etanercept subcutaneously weekly until switch to another RA therapy or up to 4.9 years. |             |

| Reporting group values                             | Tocilizumab | Etanercept | Total |
|--|-------------|------------|-------|
| Number of subjects                                 | 1538        | 1542       | 3080  |
| 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)                               | 1095        | 1087       | 2182  |
| From 65-84 years                                   | 441         | 454        | 895   |
| 85 years and over                                  | 2           | 1          | 3     |
| Age Continuous                                     |             |            |       |
| Units: Years                                       |             |            |       |
| arithmetic mean                                    | 60.7        | 60.7       |       |
| standard deviation                                 | ± 7.4       | ± 7.6      | -     |
| Gender, Male/Female                                |             |            |       |
| Units: Participants                                |             |            |       |
| Female   | 1193        | 1202       | 2395  |
| Male   | 345         | 340        | 685   |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Tocilizumab |
| Reporting group description:<br>Participants received 8 mg/kg tocilizumab IV every 4 weeks until switch to another RA therapy or up to 4.9 years.   |             |
| Reporting group title   | Etanercept  |
| Reporting group description:<br>Participants received 50 mg etanercept subcutaneously weekly until switch to another RA therapy or up to 4.9 years. |             |

### Primary: Time to first Cardiovascular (CV) Events Adjudication Committee (EAC) (CV-EAC) Adjudicated Event

|  |  |
|--|--|
| End point title  | Time to first Cardiovascular (CV) Events Adjudication Committee (EAC) (CV-EAC) Adjudicated Event |
| End point description:<br>Prospective comparison of time to first occurrence of any component of the composite of CV death (including events adjudicated as 'Undetermined Cause of Death'), non-fatal myocardial infarction, or non-fatal stroke.<br>Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline up to 4.9 years   |  |

| End point values                         | Tocilizumab     | Etanercept      |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 1538            | 1542            |  |  |
| Units: Percentage of patients with event |                 |                 |  |  |
| number (not applicable)                  | 5.4             | 5.1             |  |  |

### Statistical analyses

|   |                          |
|---|--------------------------|
| Statistical analysis title  | Cox Regression           |
| Statistical analysis description:<br>The analysis assessed in the ITT population the hazard ratio of the primary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients. A stratified Cox proportional hazards regression model was used in evaluating the relative MACE rate of TCZ over ETA, with the following randomization factors used as strata: • Previous exposure to anti-TNF (Yes/No) • History of CV events (Yes/No) |                          |
| Comparison groups   | Tocilizumab v Etanercept |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 3080              |
| Analysis specification                  | Pre-specified     |
| Analysis type                           |                   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.05              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.77              |
| upper limit                             | 1.43              |

### Primary: Time to first CV-EAC Adjudicated Event - Sensitivity Analysis

|   |   |
|---|---|
| End point title   | Time to first CV-EAC Adjudicated Event - Sensitivity Analysis |
| End point description:  |   |
| Prospective comparison of time to first occurrence of any component of the composite of CV death (including events adjudicated as 'Undetermined Cause of Death'), non-fatal myocardial infarction, or non-fatal stroke - Sensitivity Analysis.<br>Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| From Baseline up to 4.9 years   |   |

| End point values                         | Tocilizumab     | Etanercept      |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 1538            | 1542            |  |  |
| Units: Percentage of patients with event |                 |                 |  |  |
| number (not applicable)                  | 3.7             | 3.4             |  |  |

### Statistical analyses

|   |                          |
|---|--------------------------|
| Statistical analysis title  | Cox regression           |
| Statistical analysis description:   |                          |
| The analysis assessed in the OT population the hazard ratio of the primary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients. A stratified Cox proportional hazards regression model was used in evaluating the relative MACE rate of TCZ over ETA, with the following randomization factors used as strata: • Previous exposure to anti-TNF (Yes/No) • History of CV events (Yes/No) |                          |
| Comparison groups   | Tocilizumab v Etanercept |
| Number of subjects included in analysis   | 3080                     |
| Analysis specification  | Pre-specified            |
| Analysis type   |                          |
| Parameter estimate  | Hazard ratio (HR)        |
| Point estimate  | 1.11                     |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.76    |
| upper limit         | 1.62    |

### Primary: Time to first CV-EAC adjudicated event excluding undetermined cause of death - Sensitivity Analysis

|   |   |
|---|---|
| End point title   | Time to first CV-EAC adjudicated event excluding undetermined cause of death - Sensitivity Analysis |
| End point description:  |   |
| Prospective comparison of time to first occurrence of any component of the composite of CV death (excluding events adjudicated as 'Undetermined Cause of Death'), non-fatal myocardial infarction, or non-fatal stroke - Sensitivity Analyses.<br>Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| From baseline up to 4.9 years   |   |

| End point values                            | Tocilizumab     | Etanercept      |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 1538            | 1542            |  |  |
| Units: Percentage of patients with an event |                 |                 |  |  |
| number (not applicable)                     | 4.8             | 4.7             |  |  |

### Statistical analyses

|  |                          |
|--|--------------------------|
| Statistical analysis title   | Cox regression           |
| Statistical analysis description:  |                          |
| The analysis assessed in the ITT population the hazard ratio of the primary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients. A stratified Cox proportional hazards regression model was used in evaluating the relative MACE rate of TCZ over ETA, with the following randomization factors used as strata: • Previous exposure to anti-TNF (Yes/No) • History of CV events (Yes/No) |                          |
| Comparison groups  | Tocilizumab v Etanercept |
| Number of subjects included in analysis  | 3080                     |
| Analysis specification   | Pre-specified            |
| Analysis type  |                          |
| Parameter estimate   | Hazard ratio (HR)        |
| Point estimate   | 1.01                     |
| Confidence interval  |                          |
| level  | 95 %                     |
| sides  | 2-sided                  |
| lower limit  | 0.73                     |
| upper limit  | 1.4                      |

---

**Primary: Time to first CV-EAC adjudicated event before last direct contact date - Sensitivity Analysis**

---

|                 |   |
|-----------------|---|
| End point title | Time to first CV-EAC adjudicated event before last direct contact date - Sensitivity Analysis |
|-----------------|---|

**End point description:**

Prospective comparison of time to first occurrence of any component of the composite of CV death (including events adjudicated as 'Undetermined Cause of Death'), non-fatal myocardial infarction, or non-fatal stroke before last direct contact date (i.e., latest date of visit, IVRS call, or site call). Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported.

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

**End point timeframe:**

From Baseline up to 4.9 years

---

| End point values                                | Tocilizumab     | Etanercept      |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                              | Reporting group | Reporting group |  |  |
| Number of subjects analysed                     | 1538            | 1542            |  |  |
| Units: Percentage of participants with an event |                 |                 |  |  |
| number (not applicable)                         | 3.2             | 3               |  |  |

**Statistical analyses**

|                            |                |
|----------------------------|----------------|
| Statistical analysis title | Cox regression |
|----------------------------|----------------|

**Statistical analysis description:**

The analysis assessed in the ITT population the hazard ratio of the primary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients. A stratified Cox proportional hazards regression model was used in evaluating the relative MACE rate of TCZ over ETA, with the following randomization factors used as strata: • Previous exposure to anti-TNF (Yes/No) • History of CV events (Yes/No)

|   |                          |
|---|--------------------------|
| Comparison groups                       | Tocilizumab v Etanercept |
| Number of subjects included in analysis | 3080                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| Parameter estimate                      | Hazard ratio (HR)        |
| Point estimate                          | 1.04                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.7                      |
| upper limit                             | 1.56                     |

---

**Secondary: The time to first occurrence of an expanded CV composite endpoint**

---

|  |   |
|--|---|
| End point title  | The time to first occurrence of an expanded CV composite endpoint |
| End point description:   |   |
| Prospective comparison of the time to first occurrence of the expanded composite endpoint. The expanded composite endpoint is defined as the CV composite of the primary endpoint with the addition of non-elective coronary revascularization procedures and hospitalization for unstable angina. Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From baseline up to 4.9 years  |   |

| End point values                   | Tocilizumab     | Etanercept      |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 1538            | 1542            |  |  |
| Units: Percentages of participants |                 |                 |  |  |
| number (not applicable)            | 5.5             | 5.4             |  |  |

## Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Cox regression                 |
| Statistical analysis description:  |                                |
| The analysis assessed in the ITT population the hazard ratio of the secondary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients. |                                |
| A stratified Cox proportional hazards regression model was used in evaluating the relative CV event rate of TCZ over ETA, with the following randomization factors used as strata:                               |                                |
| <ul style="list-style-type: none"> <li>• Previous exposure to anti-TNF (Yes/No)</li> <li>• History of CV events (Yes/No)</li> </ul>  |                                |
| Comparison groups  | Tocilizumab v Etanercept       |
| Number of subjects included in analysis  | 3080                           |
| Analysis specification   | Pre-specified                  |
| Analysis type  | non-inferiority <sup>[1]</sup> |
| Parameter estimate   | Hazard ratio (HR)              |
| Point estimate   | 0.99                           |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | 0.73                           |
| upper limit  | 1.34                           |

Notes:

[1] - The non-inferiority margin was only formally tested for the primary ITT analysis

## Secondary: Individual component of primary endpoint: Non-fatal Myocardial Infarction

|   |   |
|---|---|
| End point title   | Individual component of primary endpoint: Non-fatal Myocardial Infarction |
| End point description:  |   |
| Prospective comparison of time to first occurrence of Individual component of primary endpoint: Non |   |

fatal Myocardial Infarction.

Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| From baseline up to 4.9 years |           |

| End point values                  | Tocilizumab     | Etanercept      |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 1538            | 1542            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 1.8             | 2               |  |  |

## Statistical analyses

|                            |                |
|----------------------------|----------------|
| Statistical analysis title | Cox regression |
|----------------------------|----------------|

Statistical analysis description:

The analysis assessed in the ITT population the hazard ratio of the secondary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients.

A stratified Cox proportional hazards regression model was used in evaluating the relative CV event rate of TCZ over ETA, with the following randomization factors used as strata:

- Previous exposure to anti-TNF (Yes/No)
- History of CV events (Yes/No)

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Tocilizumab v Etanercept       |
| Number of subjects included in analysis | 3080                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.89                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.54                           |
| upper limit                             | 1.49                           |

Notes:

[2] - The non-inferiority margin was only formally tested for the primary ITT analysis

## Secondary: Individual component of primary endpoint: cardiovascular death

|                 |  |
|-----------------|--|
| End point title | Individual component of primary endpoint: cardiovascular death |
|-----------------|--|

End point description:

Prospective comparison of time to first occurrence of Individual component of primary endpoint: cardiovascular death.

Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| From baseline up to 4.9 years |           |

| End point values                  | Tocilizumab     | Etanercept      |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 1538            | 1542            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 2.3             | 2.3             |  |  |

## Statistical analyses

| Statistical analysis title | Cox regression |
|----------------------------|----------------|
|----------------------------|----------------|

Statistical analysis description:

The analysis assessed in the ITT population the hazard ratio of the secondary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients.

A stratified Cox proportional hazards regression model was used in evaluating the relative CV event rate of TCZ over ETA, with the following randomization factors used as strata:

- Previous exposure to anti-TNF (Yes/No)
- History of CV events (Yes/No)

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Tocilizumab v Etanercept       |
| Number of subjects included in analysis | 3080                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[3]</sup> |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 1.03                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.64                           |
| upper limit                             | 1.63                           |

Notes:

[3] - The non-inferiority margin was only formally tested for the primary ITT analysis.

## Secondary: Individual component of primary endpoint: non-fatal stroke

|                 |  |
|-----------------|--|
| End point title | Individual component of primary endpoint: non-fatal stroke |
|-----------------|--|

End point description:

Prospective comparison of time to first occurrence of Individual component of primary endpoint: non-fatal stroke.

Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported.

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

End point timeframe:

From baseline up to 4.9 years

| End point values                                | Tocilizumab     | Etanercept      |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                              | Reporting group | Reporting group |  |  |
| Number of subjects analysed                     | 1538            | 1542            |  |  |
| Units: Percentage of participants with an event |                 |                 |  |  |
| number (not applicable)                         | 1.6             | 1               |  |  |

## Statistical analyses

| Statistical analysis title  | Cox regression                 |
|---|--------------------------------|
| Statistical analysis description:   |                                |
| <p>The analysis assessed in the ITT population the hazard ratio of the secondary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients.</p> <p>A stratified Cox proportional hazards regression model was used in evaluating the relative CV event rate of TCZ over ETA, with the following randomization factors used as strata:</p> <ul style="list-style-type: none"> <li>• Previous exposure to anti-TNF (Yes/No)</li> <li>• History of CV events (Yes/No)</li> </ul> |                                |
| Comparison groups   | Tocilizumab v Etanercept       |
| Number of subjects included in analysis   | 3080                           |
| Analysis specification  | Pre-specified                  |
| Analysis type   | non-inferiority <sup>[4]</sup> |
| Parameter estimate  | Hazard ratio (HR)              |
| Point estimate  | 1.53                           |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | 0.8                            |
| upper limit   | 2.92                           |

Notes:

[4] - The non-inferiority margin was only formally tested for the primary ITT analysis

## Secondary: Individual component of primary endpoint: All-cause mortality

|  |   |
|--|---|
| End point title  | Individual component of primary endpoint: All-cause mortality |
| End point description:   |   |
| <p>Prospective comparison of time to first occurrence of Individual component of primary endpoint: All-cause mortality.</p> <p>Median time to event and 95% confidence intervals could not be estimated due to less than 50% of patients experiencing an event; percentage of patients with event is reported.</p> |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From baseline up to 4.9 years  |   |

| End point values                  | Tocilizumab     | Etanercept      |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 1538            | 1542            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 4.2             | 4.2             |  |  |

## Statistical analyses

| Statistical analysis title | Cox regression |
|----------------------------|----------------|
|----------------------------|----------------|

Statistical analysis description:

The analysis assessed in the ITT population the hazard ratio of the secondary endpoint in TCZ compared to ETA patients. This was done through a comparison of the hazard functions between TCZ and ETA patients.

A stratified Cox proportional hazards regression model was used in evaluating the relative CV event rate of TCZ over ETA, with the following randomization factors used as strata:

- Previous exposure to anti-TNF (Yes/No)
- History of CV events (Yes/No)

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Tocilizumab v Etanercept       |
| Number of subjects included in analysis | 3080                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[5]</sup> |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.99                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.7                            |
| upper limit                             | 1.41                           |

Notes:

[5] - The non-inferiority margin was only formally tested for the primary ITT analysis.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected throughout the entire course of the study.

Adverse event reporting additional description:

Analyses were conducted on the On treatment safety (OTS) population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Etanercept |
|-----------------------|------------|

Reporting group description:

Participants received 50 mg etanercept subcutaneously weekly until switch to another RA therapy or up to 4.9 years.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Tocilizumab |
|-----------------------|-------------|

Reporting group description:

Participants received 8 mg/kg tocilizumab IV every 4 weeks until switch to another RA therapy or up to 4.9 years.

| Serious adverse events  | Etanercept             | Tocilizumab            |  |
|---|------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                        |                        |  |
| subjects affected / exposed   | 422 / 1542<br>(27.37%) | 479 / 1538<br>(31.14%) |  |
| number of deaths (all causes)                                       | 69                     | 67                     |  |
| number of deaths resulting from adverse events                      | 10                     | 14                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |  |
| ADENOCARCINOMA  |                        |                        |  |
| subjects affected / exposed   | 1 / 1542 (0.06%)       | 0 / 1538 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 1 / 1                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| ADENOCARCINOMA OF COLON   |                        |                        |  |
| subjects affected / exposed   | 2 / 1542 (0.13%)       | 0 / 1538 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 2                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| ANAL SQUAMOUS CELL CARCINOMA  |                        |                        |  |
| subjects affected / exposed   | 1 / 1542 (0.06%)       | 0 / 1538 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| BASAL CELL CARCINOMA                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BENIGN ANORECTAL NEOPLASM                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BENIGN NEOPLASM OF CERVIX UTERI                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BLADDER CANCER                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| BLADDER TRANSITIONAL CELL CARCINOMA             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRAIN NEOPLASM                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| BREAST CANCER                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| CARCINOID TUMOUR OF THE GASTROINTESTINAL TRACT  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| CARCINOID TUMOUR PULMONARY                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CARDIAC MYXOMA                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CENTRAL NERVOUS SYSTEM LYMPHOMA                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CEREBRAL HAEMANGIOMA                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CHOLANGIOCARCINOMA                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| COLON ADENOMA                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLON CANCER                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLON CANCER METASTATIC                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| COLORECTAL CANCER                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>DIFFUSE LARGE B–CELL LYMPHOMA</b>            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ENDOMETRIAL ADENOCARCINOMA</b>               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>GLIOBLASTOMA</b>                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HAEMANGIOMA</b>                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>INTESTINAL ADENOCARCINOMA</b>                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>INTRADUCTAL PROLIFERATIVE BREAST LESION</b>  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>LARYNGEAL CANCER</b>                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>LUNG ADENOCARCINOMA</b>                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| LUNG ADENOCARCINOMA STAGE IV                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| LUNG CANCER METASTATIC                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| LUNG NEOPLASM                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| LUNG NEOPLASM MALIGNANT                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2            | 1 / 3            |  |
| MALIGNANT MELANOMA STAGE II                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MARJOLIN'S ULCER                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| METASTASES TO BONE                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| METASTATIC GASTRIC CANCER                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>METASTATIC NEOPLASM</b>                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>NEOPLASM MALIGNANT</b>                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>NON-HODGKIN'S LYMPHOMA</b>                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>OVARIAN ADENOMA</b>                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>OVARIAN CANCER</b>                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| <b>PANCREATIC CARCINOMA METASTATIC</b>          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| <b>PANCREATIC NEOPLASM</b>                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>PAPILLARY THYROID CANCER</b>                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PARAPROTEINAEMIA                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PARATHYROID TUMOUR BENIGN                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PHARYNGEAL NEOPLASM BENIGN                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PITUITARY TUMOUR BENIGN                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PLASMA CELL MYELOMA                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PROSTATE CANCER                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RENAL CANCER                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RENAL CELL CARCINOMA                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SMALL CELL LUNG CANCER                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SQUAMOUS CELL CARCINOMA OF LUNG                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SQUAMOUS CELL CARCINOMA OF THE TONGUE           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SQUAMOUS ENDOMETRIAL CARCINOMA                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| THYROID ADENOMA                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TUMOUR INVASION                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| UTERINE CANCER                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Vascular disorders                              |                  |                  |  |
| AORTIC ANEURYSM                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| AORTIC ANEURYSM RUPTURE                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| AORTIC CALCIFICATION                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| AORTIC DISSECTION                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| AORTIC STENOSIS                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 8 / 1542 (0.52%) | 6 / 1538 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| EMBOLISM ARTERIAL                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FEMORAL ARTERY EMBOLISM                         |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMATOMA                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERTENSION                                    |                  |                  |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERTENSIVE CRISIS                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERTENSIVE EMERGENCY                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPOTENSION                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INFARCTION                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ORTHOSTATIC HYPOTENSION                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PERIPHERAL ARTERIAL OCCLUSIVE DISEASE           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PERIPHERAL ISCHAEMIA                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PERIPHERAL VENOUS DISEASE                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| RHEUMATOID VASCULITIS                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUBCLAVIAN ARTERY OCCLUSION                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| THROMBOSIS                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VARICOSE VEIN                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VENOUS THROMBOSIS LIMB                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| ABDOMINAL HERNIA REPAIR                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ANAL FISTULA EXCISION                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ANGIOPLASTY                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| APPENDICECTOMY                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CARDIAC PACEMAKER REPLACEMENT                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLOSTOMY CLOSURE                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HIP ARTHROPLASTY                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| IMPLANTABLE DEFIBRILLATOR INSERTION             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| KNEE ARTHROPLASTY                               |                  |                  |  |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| subjects affected / exposed                          | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| LARGE INTESTINE ANASTOMOSIS                          |                   |                  |  |
| subjects affected / exposed                          | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| MITRAL VALVE REPLACEMENT                             |                   |                  |  |
| subjects affected / exposed                          | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| SEQUESTRECTOMY                                       |                   |                  |  |
| subjects affected / exposed                          | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| UMBILICAL HERNIA REPAIR                              |                   |                  |  |
| subjects affected / exposed                          | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| General disorders and administration site conditions |                   |                  |  |
| CHEST PAIN   |                   |                  |  |
| subjects affected / exposed                          | 10 / 1542 (0.65%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all      | 0 / 10            | 0 / 3            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            |  |
| COMPLICATION ASSOCIATED WITH DEVICE                  |                   |                  |  |
| subjects affected / exposed                          | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| 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 / 1542 (0.26%)  | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all      | 0 / 4             | 0 / 3            |  |
| deaths causally related to treatment / all           | 0 / 4             | 0 / 3            |  |
| GENERAL PHYSICAL HEALTH                              |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| DETERIORATION                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| IMPAIRED HEALING                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LOCAL SWELLING                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| NON-CARDIAC CHEST PAIN                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OEDEMA PERIPHERAL                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PAIN  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| PYREXIA   |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUDDEN DEATH                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |  |
| SWELLING  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Immune system disorders                         |                  |                  |  |
| DRUG HYPERSENSITIVITY                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERSENSITIVITY                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OVERLAP SYNDROME                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SARCOIDOSIS                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| ACQUIRED PHIMOSIS                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BREAST FIBROSIS                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| CERVICAL POLYP                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CERVICAL DYSPLASIA                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CYSTOCELE                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GENITAL PROLAPSE                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| METRORRHAGIA                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OVARIAN CYST TORSION                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SPERMATOCELE                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RECTOCELE                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| UTERINE POLYP                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| UTERINE PROLAPSE                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VAGINAL HAEMATOMA                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ACUTE RESPIRATORY DISTRESS SYNDROME             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ALVEOLITIS                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ASTHMA  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 1542 (0.32%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ASTHMATIC CRISIS                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ATELECTASIS                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHIAL HYPERREACTIVITY                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHIAL OBSTRUCTION                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHITIS CHRONIC                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHOSPASM                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHOSTENOSIS                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE           |                  |                  |  |

|   |                  |                   |
|---|------------------|-------------------|
| subjects affected / exposed                     | 7 / 1542 (0.45%) | 10 / 1538 (0.65%) |
| occurrences causally related to treatment / all | 2 / 7            | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2             |
| CHRONIC RESPIRATORY FAILURE                     |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| DYSпноEA  |                  |                   |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 5 / 1538 (0.33%)  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| EMPHYSEMA                                       |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| EPISTAXIS                                       |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| HYDROTHORAX                                     |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| HYPOXIA   |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| INTERSTITIAL LUNG DISEASE                       |                  |                   |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 5 / 1538 (0.33%)  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| LUNG DISORDER                                   |                  |                   |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| LUNG INFILTRATION                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| PLEURAL EFFUSION                                |                   |                  |  |
| subjects affected / exposed                     | 5 / 1542 (0.32%)  | 6 / 1538 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 6             | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| PNEUMONIA ASPIRATION                            |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| PNEUMONITIS                                     |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| PNEUMOTHORAX                                    |                   |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| PULMONARY EMBOLISM                              |                   |                  |  |
| subjects affected / exposed                     | 11 / 1542 (0.71%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 2 / 11            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 2             | 0 / 0            |  |
| PULMONARY FIBROSIS                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| PULMONARY GRANULOMA                             |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY HYPERTENSION                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY MASS                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY OEDEMA                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY SARCOIDOSIS                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY THROMBOSIS                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| RESPIRATORY DISTRESS                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RESPIRATORY FAILURE                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 2 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| BURNOUT SYNDROME                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CONFUSIONAL STATE                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DELIRIUM  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DELIRIUM TREMENS                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DEPRESSION                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MAJOR DEPRESSION                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MENTAL DISORDER                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MENTAL STATUS CHANGES                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PSYCHOTIC DISORDER                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SCHIZOAFFECTIVE DISORDER<br>BIPOLAR TYPE        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUICIDAL IDEATION                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUICIDE ATTEMPT                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MANIA   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| DEVICE BREAKAGE                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DEVICE DISLOCATION                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DEVICE FAILURE                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DEVICE LOOSENING                                |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>Hepatobiliary disorders</b>                  |                  |                   |  |
| <b>BILE DUCT OBSTRUCTION</b>                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>CHOLANGITIS ACUTE</b>                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>CHOLECYSTITIS</b>                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>CHOLECYSTITIS ACUTE</b>                      |                  |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>CHOLECYSTITIS CHRONIC</b>                    |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>CHOLELITHIASIS</b>                           |                  |                   |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 14 / 1538 (0.91%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>HEPATIC VEIN THROMBOSIS</b>                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| <b>HEPATITIS</b>                                |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HEPATITIS ACUTE                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| POST CHOLECYSTECTOMY SYNDROME                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| EOSINOPHIL COUNT INCREASED                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMATOCRIT ABNORMAL                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMOGLOBIN ABNORMAL                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LIVER FUNCTION TEST INCREASED                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| STAPHYLOCOCCUS TEST POSITIVE                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SYNOVIAL FLUID WHITE BLOOD CELLS POSITIVE       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TRANSAMINASES INCREASED                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TROPONIN INCREASED                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| ACCIDENT AT WORK                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| ANAEMIA POSTOPERATIVE                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ANKLE FRACTURE                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ARTHROPOD STING                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| COMMINUTED FRACTURE                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CONTUSION                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DISLOCATION OF VERTEBRA                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| FALL  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FEMORAL NECK FRACTURE                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FEMUR FRACTURE                                  |                  |                  |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FOOT FRACTURE                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FRACTURE DISPLACEMENT                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| HAND FRACTURE                                   |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| HIP FRACTURE                                    |                   |                  |  |
| subjects affected / exposed                     | 12 / 1542 (0.78%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| HUMERUS FRACTURE                                |                   |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%)  | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| INFUSION RELATED REACTION                       |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| JOINT DISLOCATION                               |                   |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| JOINT INJURY                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| LIGAMENT INJURY                                 |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| LOWER LIMB FRACTURE                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| OVERDOSE  |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PNEUMOTHORAX TRAUMATIC                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| POST PROCEDURAL FISTULA                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RADIUS FRACTURE                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RESPIRATORY FUME INHALATION DISORDER            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 4 / 1542 (0.26%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SPINAL COMPRESSION FRACTURE                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SPINAL FRACTURE                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| STOMAL HERNIA                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| STRESS FRACTURE                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUBCUTANEOUS HAEMATOMA                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUBDURAL HAEMATOMA                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 20           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SYNOVIAL RUPTURE                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TENDON RUPTURE                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| THORACIC VERTEBRAL FRACTURE                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ULNA FRACTURE                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| UPPER LIMB FRACTURE                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| WOUND   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| WOUND DEHISCENCE                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| WRIST FRACTURE                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| ATRIAL SEPTAL DEFECT                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYDROCELE                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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 / 1542 (0.06%)  | 1 / 1538 (0.07%)  |  |
| 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                     | 9 / 1542 (0.58%)  | 7 / 1538 (0.46%)  |  |
| occurrences causally related to treatment / all | 1 / 9             | 1 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| ADAMS–STOKES SYNDROME                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ANGINA PECTORIS                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 8 / 1538 (0.52%)  |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ANGINA UNSTABLE                                 |                   |                   |  |
| subjects affected / exposed                     | 7 / 1542 (0.45%)  | 4 / 1538 (0.26%)  |  |
| occurrences causally related to treatment / all | 0 / 10            | 2 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ATRIAL FIBRILLATION                             |                   |                   |  |
| subjects affected / exposed                     | 18 / 1542 (1.17%) | 14 / 1538 (0.91%) |  |
| occurrences causally related to treatment / all | 3 / 23            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ATRIAL FLUTTER                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 2 / 1538 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ATRIOVENTRICULAR BLOCK SECOND DEGREE            |                   |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| BRADYARRHYTHMIA                                 |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| BRADYCARDIA                                     |                  |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| BUNDLE BRANCH BLOCK LEFT                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CARDIAC ARREST                                  |                  |                   |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 1             |  |
| CARDIAC FAILURE                                 |                  |                   |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 11 / 1538 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 5 / 16            |  |
| deaths causally related to treatment / all      | 0 / 1            | 1 / 3             |  |
| CARDIAC FAILURE CHRONIC                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| CARDIAC FAILURE CONGESTIVE                      |                  |                   |  |
| subjects affected / exposed                     | 8 / 1542 (0.52%) | 7 / 1538 (0.46%)  |  |
| occurrences causally related to treatment / all | 2 / 11           | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1             |  |
| CARDIAC FIBRILLATION                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CARDIAC TAMPONADE                               |                  |                   |  |



|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| CARDIOGENIC SHOCK                               |                  |                  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| CARDIOMYOPATHY                                  |                  |                  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| CARDIOPULMONARY FAILURE                         |                  |                  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 4 / 1538 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 4            |
| CORONARY ARTERY DISEASE                         |                  |                  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 9 / 1538 (0.59%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| CORONARY ARTERY OCCLUSION                       |                  |                  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |
| CORONARY ARTERY STENOSIS                        |                  |                  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| HYPERTENSIVE HEART DISEASE                      |                  |                  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| ISCHAEMIC CARDIOMYOPATHY                        |                  |                  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| LEFT VENTRICULAR FAILURE                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| MITRAL VALVE INCOMPETENCE                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| MITRAL VALVE STENOSIS                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| 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                     | 15 / 1542 (0.97%) | 10 / 1538 (0.65%) |  |
| occurrences causally related to treatment / all | 2 / 15            | 0 / 10            |  |
| deaths causally related to treatment / all      | 1 / 5             | 0 / 1             |  |
| MYOCARDIAL ISCHAEMIA                            |                   |                   |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 1 / 1             |  |
| PALPITATIONS                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| POSTINFARCTION ANGINA                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| 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                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SINOATRIAL BLOCK                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SINUS BRADYCARDIA                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SINUS NODE DYSFUNCTION                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SUPRAVENTRICULAR TACHYCARDIA                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TACHYCARDIA                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VENTRICULAR DYSFUNCTION                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VENTRICULAR FIBRILLATION                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VENTRICULAR TACHYCARDIA                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CARDIO-RESPIRATORY ARREST                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 1            |  |
| Nervous system disorders                        |                  |                  |  |
| AMYOTROPHIC LATERAL SCLEROSIS                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BALANCE DISORDER                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRAIN STEM INFARCTION                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CAROTID ARTERY DISEASE                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CAROTID ARTERY STENOSIS                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CEREBRAL HAEMATOMA                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CEREBRAL INFARCTION                             |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CEREBRAL ISCHAEMIA                              |                  |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CEREBROVASCULAR ACCIDENT                        |                  |                   |  |
| subjects affected / exposed                     | 8 / 1542 (0.52%) | 14 / 1538 (0.91%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 2 / 15            |  |
| deaths causally related to treatment / all      | 0 / 3            | 1 / 3             |  |
| CEREBROVASCULAR DISORDER                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CERVICAL CORD COMPRESSION                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| CERVICAL RADICULOPATHY                          |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| COMA  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| DEMENTIA  |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| DEMENTIA ALZHEIMER'S TYPE                       |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| DIABETIC COMA                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DYSARTHRIA                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DYSKINESIA                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| EMBOLIC STROKE                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ENCEPHALOPATHY                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| EPILEPSY  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FACIAL PARALYSIS                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GENERALISED TONIC–CLONIC SEIZURE                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMORRHAGIC STROKE                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| HEMIPARESIS                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HEPATIC ENCEPHALOPATHY                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERTENSIVE ENCEPHALOPATHY                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INTRACRANIAL ANEURYSM                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ISCHAEMIC STROKE                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 1542 (0.32%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| LOSS OF CONSCIOUSNESS                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUMBAR RADICULOPATHY                            |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                      | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>METABOLIC ENCEPHALOPATHY</b>                  |                  |                  |  |
| subjects affected / exposed                      | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>MIGRAINE</b>                                  |                  |                  |  |
| subjects affected / exposed                      | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all  | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>MYASTHENIA GRAVIS</b>                         |                  |                  |  |
| subjects affected / exposed                      | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>PARAESTHESIA</b>                              |                  |                  |  |
| subjects affected / exposed                      | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>PARKINSON'S DISEASE</b>                       |                  |                  |  |
| subjects affected / exposed                      | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>PRESYNCOPE</b>                                |                  |                  |  |
| subjects affected / exposed                      | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>REVERSIBLE ISCHAEMIC NEUROLOGICAL DEFICIT</b> |                  |                  |  |
| subjects affected / exposed                      | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0            | 0 / 0            |  |
| <b>RUPTURED CEREBRAL ANEURYSM</b>                |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SCIATICA  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SEIZURE   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SPINAL CORD COMPRESSION                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| SUBARACHNOID HAEMORRHAGE                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| SYNCOPE   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TRANSIENT GLOBAL AMNESIA                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TRANSIENT ISCHAEMIC ATTACK                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 9 / 1538 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VASCULAR DEMENTIA                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| <b>Blood and lymphatic system disorders</b>     |                  |                  |  |
| <b>ANAEMIA</b>                                  |                  |                  |  |
| subjects affected / exposed                     | 9 / 1542 (0.58%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| <b>AUTOIMMUNE HAEMOLYTIC ANAEMIA</b>            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>COAGULOPATHY</b>                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>GRANULOCYTOPENIA</b>                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>LEUKOCYTOSIS</b>                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>MICROCYTIC ANAEMIA</b>                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>PANCYTOPENIA</b>                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>THROMBOCYTOPENIA</b>                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LEUKOPENIA                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| DEAFNESS UNILATERAL                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VERTIGO   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| CATARACT  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CORNEAL PERFORATION                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| KERATITIS                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RETINAL DETACHMENT                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SCLERITIS</b>                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ULCERATIVE KERATITIS</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Gastrointestinal disorders</b>               |                  |                  |  |
| <b>ABDOMINAL ADHESIONS</b>                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ABDOMINAL HERNIA</b>                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ABDOMINAL PAIN</b>                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| <b>ABDOMINAL PAIN UPPER</b>                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ACID PEPTIC DISEASE</b>                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>ACUTE ABDOMEN</b>                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| ASCITES   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLITIS   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLITIS ISCHAEMIC                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COLITIS ULCERATIVE                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CONSTIPATION                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CROHN'S DISEASE                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIAPHRAGMATIC HERNIA                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIARRHOEA                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIVERTICULAR PERFORATION                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 6 / 1538 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 6 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIVERTICULUM                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIVERTICULUM INTESTINAL                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIVERTICULUM INTESTINAL HAEMORRHAGIC            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DUODENAL ULCER                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ENTERITIS                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ENTEROCOLITIS                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FEMORAL HERNIA                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTRIC ULCER HAEMORRHAGE                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTRIC ULCER                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTRIC ULCER PERFORATION                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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 / 1542 (0.13%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTROINTESTINAL HAEMORRHAGE                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| GASTRITIS HAEMORRHAGIC                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTROINTESTINAL INFLAMMATION                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTROINTESTINAL ULCER HAEMORRHAGE              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GASTROESOPHAGEAL REFLUX DISEASE                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMATEMESIS                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| HAEMATOCHESIA                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INCARCERATED HIATUS HERNIA                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMORRHOIDS                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INCARCERATED UMBILICAL HERNIA                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INGUINAL HERNIA                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INTESTINAL OBSTRUCTION                          |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LARGE INTESTINAL STENOSIS                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LARGE INTESTINE PERFORATION                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LARGE INTESTINE POLYP                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LOWER GASTROINTESTINAL HAEMORRHAGE              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MALLORY–WEISS SYNDROME                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MELAENA   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| NAUSEA  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OESOPHAGITIS                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PALATAL DISORDER                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PANCREATITIS                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PANCREATITIS ACUTE                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| PEPTIC ULCER                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PEPTIC ULCER HAEMORRHAGE                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| RETROPERITONEAL FIBROSIS                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| UPPER GASTROINTESTINAL HAEMORRHAGE              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| VOMITING  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| ANGIOEDEMA                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BLISTER   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DECUBITUS ULCER                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DERMAL CYST                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DERMATITIS                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIABETIC FOOT                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERSENSITIVITY VASCULITIS                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| PEMPHIGOID                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RASH  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RASH ERYTHEMATOUS                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SKIN DISORDER                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SKIN NECROSIS                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| SKIN ULCER                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 4 / 1538 (0.26%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 2 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| URTICARIA                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VASCULITIC ULCER                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 5 / 1542 (0.32%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CALCULUS BLADDER                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CHRONIC KIDNEY DISEASE                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| CYSTITIS HAEMORRHAGIC                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| END STAGE RENAL DISEASE                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| GLOMERULONEPHRITIS CHRONIC                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYDRONEPHROSIS                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| NEPHROLITHIASIS                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OBSTRUCTIVE NEPHROPATHY                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PELVI-URETERIC OBSTRUCTION                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| RENAL FAILURE                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| TUBULOINTERSTITIAL NEPHRITIS                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| URETERIC OBSTRUCTION                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| URETEROLITHIASIS                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| URETHRAL STENOSIS                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| GOITRE  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPERTHYROIDISM                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HYPOTHYROIDISM                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| ARTHRALGIA                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ARTHRITIS                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BACK PAIN                                       |                  |                  |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| BURSITIS  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| COSTOCHONDRITIS                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FASCIITIS                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FINGER DEFORMITY                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FISTULA   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| FOOT DEFORMITY                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| HAEMARTHROSIS                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INTERVERTEBRAL DISC DISORDER                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INTERVERTEBRAL DISC PROTRUSION                  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| KNEE DEFORMITY                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LIMB DEFORMITY                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUMBAR SPINAL STENOSIS                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MORPHOEA  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MUSCLE SPASMS                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MUSCULOSKELETAL CHEST PAIN                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MYALGIA   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| NECK PAIN                                       |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| OSTEOARTHRITIS                                  |                   |                   |  |
| subjects affected / exposed                     | 22 / 1542 (1.43%) | 14 / 1538 (0.91%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| OSTEONECROSIS                                   |                   |                   |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%)  | 2 / 1538 (0.13%)  |  |
| occurrences causally related to treatment / all | 1 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| OSTEONECROSIS OF JAW                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| OSTEOPOROSIS                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| OSTEOPOROTIC FRACTURE                           |                   |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| PAIN IN EXTREMITY                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| PERIARTHRITIS                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| RHEUMATOID ARTHRITIS                            |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 15 / 1542 (0.97%) | 12 / 1538 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 2 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| RHEUMATOID NODULE                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| ROTATOR CUFF SYNDROME                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| SPINAL OSTEOARTHRITIS                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| SPONDYLOLISTHESIS                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| SYNOVIAL CYST                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| SYNOVITIS                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| TENOSYNOVITIS                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (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                     |                   |                   |  |
| ABSCCESS  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ABSCCESS LIMB                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 6 / 1538 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 3 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ABSCCESS ORAL                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ABSCCESS RUPTURE                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ACUTE SINUSITIS                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ANAL ABSCESS                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| APPENDICITIS                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ARTHRITIS BACTERIAL                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 9 / 1538 (0.59%) |  |
| occurrences causally related to treatment / all | 5 / 7            | 3 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ARTHRITIS INFECTIVE                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ASPERGILLUS INFECTION                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| ATYPICAL PNEUMONIA                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BILIARY SEPSIS                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHITIS                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHITIS VIRAL                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BRONCHOPULMONARY ASPERGILLOSIS                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| BURSITIS INFECTIVE                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| CELLULITIS                                      |                  |                  |  |

|   |                  |                   |
|---|------------------|-------------------|
| subjects affected / exposed                     | 8 / 1542 (0.52%) | 24 / 1538 (1.56%) |
| occurrences causally related to treatment / all | 5 / 8            | 13 / 26           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CELLULITIS STAPHYLOCOCCAL                       |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CELLULITIS STREPTOCOCCAL                        |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CERVICITIS                                      |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CHRONIC TONSILLITIS                             |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CLOSTRIDIUM DIFFICILE COLITIS                   |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| CLOSTRIDIUM DIFFICILE INFECTION                 |                  |                   |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| COLONIC ABSCESS                                 |                  |                   |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |
| DENGUE FEVER                                    |                  |                   |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| DEVICE RELATED INFECTION                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| DEVICE RELATED SEPSIS                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| DISSEMINATED TUBERCULOSIS                       |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0             |  |
| DIVERTICULITIS                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 10 / 1538 (0.65%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 5 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| EMPHYEMA  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ENDOPHTHALMITIS                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ENTERITIS INFECTIOUS                            |                  |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| EPIDIDYMITIS                                    |                  |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| EPIGLOTTITIS                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ERYSIPELAS                                      |                  |                   |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 11 / 1538 (0.72%) |  |
| occurrences causally related to treatment / all | 3 / 4            | 3 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ESCHERICHIA PYELONEPHRITIS                      |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ESCHERICHIA SEPSIS                              |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| ESCHERICHIA URINARY TRACT INFECTION             |                  |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| FUNGAL SKIN INFECTION                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| GASTROENTERITIS                                 |                  |                   |  |
| subjects affected / exposed                     | 6 / 1542 (0.39%) | 3 / 1538 (0.20%)  |  |
| occurrences causally related to treatment / all | 2 / 6            | 2 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| GASTROENTERITIS NOROVIRUS                       |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>GASTROENTERITIS VIRAL</b>                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>GROIN ABSCESS</b>                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HAEMATOMA INFECTION</b>                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HAEMOPHILUS SEPSIS</b>                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HERPANGINA</b>                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HERPES ZOSTER</b>                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 4 / 4            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>INFECTED DERMAL CYST</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>INFECTION</b>                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INFECTIOUS COLITIS                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INFECTIOUS PLEURAL EFFUSION                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INFECTIVE ANEURYSM                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INFLUENZA                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INJECTION SITE ABSCESS                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| INTERVERTEBRAL DISCITIS                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| 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 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LOWER RESPIRATORY TRACT INFECTION               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUDWIG ANGINA                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUNG ABSCESS                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUNG INFECTION                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| LUNG INFECTION PSEUDOMONAL                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MASTOIDITIS                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MENINGITIS                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| MUSCLE ABSCESS                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| NASAL ABSCESS                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| NEUROSYPHILIS                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OESOPHAGEAL CANDIDIASIS                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OPHTHALMIC HERPES SIMPLEX                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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                     | 1 / 1542 (0.06%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OSTEOMYELITIS                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OSTEOMYELITIS CHRONIC                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| OTITIS EXTERNA                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PAPILLOMA VIRAL INFECTION                       |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| PERIHEPATIC ABSCESS                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| PERITONITIS                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 3 / 1538 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| PERITONSILLAR ABSCESS                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (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 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| PNEUMOCYSTIS JIROVECI<br>PNEUMONIA              |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 1 / 1             | 0 / 0             |  |
| PNEUMONIA                                       |                   |                   |  |
| subjects affected / exposed                     | 41 / 1542 (2.66%) | 47 / 1538 (3.06%) |  |
| occurrences causally related to treatment / all | 18 / 46           | 20 / 53           |  |
| deaths causally related to treatment / all      | 0 / 6             | 4 / 8             |  |
| PNEUMONIA BACTERIAL                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| PNEUMONIA INFLUENZAL                            |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PNEUMONIA MYCOPLASMAL                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PNEUMONIA PNEUMOCOCCAL                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PNEUMONIA STAPHYLOCOCCAL                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PNEUMONIA VIRAL                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| POST PROCEDURAL INFECTION                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| POSTOPERATIVE WOUND INFECTION                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PSEUDOMONAS INFECTION                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| PULMONARY TUBERCULOMA                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>PULMONARY TUBERCULOSIS</b>                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>PYELONEPHRITIS</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>RECTAL ABSCESS</b>                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>RESPIRATORY TRACT INFECTION</b>              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SALPINGITIS</b>                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SCROTAL ABSCESS</b>                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SEPSIS</b>                                   |                  |                  |  |
| subjects affected / exposed                     | 7 / 1542 (0.45%) | 6 / 1538 (0.39%) |  |
| occurrences causally related to treatment / all | 2 / 7            | 2 / 6            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| <b>SEPTIC SHOCK</b>                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 3 / 1538 (0.20%) |  |
| occurrences causally related to treatment / all | 3 / 4            | 2 / 3            |  |
| deaths causally related to treatment / all      | 1 / 2            | 2 / 3            |  |
| <b>SINUSITIS</b>                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SOFT TISSUE INFECTION</b>                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>STAPHYLOCOCCAL INFECTION</b>                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>STAPHYLOCOCCAL SEPSIS</b>                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>STREPTOCOCCAL BACTERAEMIA</b>                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>SUBCUTANEOUS ABSCESS</b>                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 2 / 1538 (0.13%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>TONGUE ABSCESS</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>TONSILLITIS</b>                              |                  |                  |  |



|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| TOXIC SHOCK SYNDROME<br>STREPTOCOCCAL           |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| TRACHEITIS                                      |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| TUBERCULOSIS                                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| UPPER RESPIRATORY TRACT<br>INFECTION            |                   |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| URINARY TRACT INFECTION                         |                   |                  |  |
| subjects affected / exposed                     | 12 / 1542 (0.78%) | 7 / 1538 (0.46%) |  |
| occurrences causally related to treatment / all | 6 / 13            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| URINARY TRACT INFECTION<br>BACTERIAL            |                   |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| UROSEPSIS                                       |                   |                  |  |
| subjects affected / exposed                     | 2 / 1542 (0.13%)  | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 2 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| VIRAL INFECTION                                 |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| VIRAL PHARYNGITIS                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| WEST NILE VIRAL INFECTION                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| WOUND INFECTION                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| DEHYDRATION                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 1542 (0.26%) | 5 / 1538 (0.33%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 1 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIABETES MELLITUS                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1542 (0.00%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| DIABETIC COMPLICATION                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| ELECTROLYTE IMBALANCE                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (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 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HYPERKALAEMIA</b>                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HYPOKALAEMIA</b>                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>HYPONATRAEMIA</b>                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 1542 (0.19%) | 1 / 1538 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>METABOLIC ACIDOSIS</b>                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>TYPE 2 DIABETES MELLITUS</b>                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1542 (0.06%) | 0 / 1538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Etanercept          | Tocilizumab          |  |
|---|---------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                     |                      |  |
| subjects affected / exposed                           | 910 / 1542 (59.01%) | 1090 / 1538 (70.87%) |  |
| Investigations  |                     |                      |  |
| ALANINE AMINOTRANSFERASE INCREASED                    |                     |                      |  |
| subjects affected / exposed                           | 44 / 1542 (2.85%)   | 120 / 1538 (7.80%)   |  |
| occurrences (all)                                     | 48                  | 156                  |  |

|  |  |   |  |
|--|--|---|--|
| Vascular disorders<br>HYPERTENSION<br>subjects affected / exposed<br>occurrences (all)   | 158 / 1542<br>(10.25%)<br>178  | 200 / 1538<br>(13.00%)<br>268   |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)   | 68 / 1542 (4.41%)<br>79  | 103 / 1538 (6.70%)<br>132   |  |
| Blood and lymphatic system disorders<br>LEUKOPENIA<br>subjects affected / exposed<br>occurrences (all)<br><br>NEUTROPENIA<br>subjects affected / exposed<br>occurrences (all)  | 21 / 1542 (1.36%)<br>32<br><br>33 / 1542 (2.14%)<br>49                                     | 85 / 1538 (5.53%)<br>128<br><br>92 / 1538 (5.98%)<br>153                                    |  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)  | 84 / 1542 (5.45%)<br>94  | 140 / 1538 (9.10%)<br>182   |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)   | 76 / 1542 (4.93%)<br>87  | 127 / 1538 (8.26%)<br>147   |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)<br><br>BACK PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>RHEUMATOID ARTHRITIS<br>subjects affected / exposed<br>occurrences (all) | 106 / 1542 (6.87%)<br>166<br><br>92 / 1542 (5.97%)<br>104<br><br>132 / 1542 (8.56%)<br>179 | 143 / 1538 (9.30%)<br>209<br><br>147 / 1538 (9.56%)<br>176<br><br>152 / 1538 (9.88%)<br>246 |  |
| Infections and infestations<br>BRONCHITIS<br>subjects affected / exposed<br>occurrences (all)  | 185 / 1542<br>(12.00%)<br>249  | 244 / 1538<br>(15.86%)<br>337   |  |

|                                    |                     |                     |  |
|------------------------------------|---------------------|---------------------|--|
| NASOPHARYNGITIS                    |                     |                     |  |
| subjects affected / exposed        | 141 / 1542 (9.14%)  | 239 / 1538 (15.54%) |  |
| occurrences (all)                  | 181                 | 386                 |  |
| PHARYNGITIS                        |                     |                     |  |
| subjects affected / exposed        | 76 / 1542 (4.93%)   | 113 / 1538 (7.35%)  |  |
| occurrences (all)                  | 98                  | 146                 |  |
| SINUSITIS                          |                     |                     |  |
| subjects affected / exposed        | 78 / 1542 (5.06%)   | 88 / 1538 (5.72%)   |  |
| occurrences (all)                  | 103                 | 124                 |  |
| UPPER RESPIRATORY TRACT INFECTION  |                     |                     |  |
| subjects affected / exposed        | 193 / 1542 (12.52%) | 243 / 1538 (15.80%) |  |
| occurrences (all)                  | 291                 | 425                 |  |
| URINARY TRACT INFECTION            |                     |                     |  |
| subjects affected / exposed        | 150 / 1542 (9.73%)  | 174 / 1538 (11.31%) |  |
| occurrences (all)                  | 200                 | 243                 |  |
| Metabolism and nutrition disorders |                     |                     |  |
| HYPERCHOLESTEROLAEMIA              |                     |                     |  |
| subjects affected / exposed        | 52 / 1542 (3.37%)   | 143 / 1538 (9.30%)  |  |
| occurrences (all)                  | 55                  | 158                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 14 January 2011 | <ul style="list-style-type: none"><li>- Removal of the interim analysis</li><li>- Inclusion of stroke of all classifications</li><li>- "Premature withdrawal" and "Minimal telephone follow up upon withdrawal from active participation" related info were split in two different sections</li><li>- Hypersensitivity reactions and Immunogenicity assessment: treatment recommendations were removed from the protocol to allow health care providers to include all therapies available according to the standard of care appropriate for the patient's reaction</li><li>- Decision about monitoring compliance with home-administered etanercept to be assessed using Interactive Voice Response System (IVRS) and used syringe counts.</li><li>- Revision of the process for identifying and reporting cardiovascular events for adjudication</li><li>- Sponsor's decision not to collect biomarkers</li></ul>   |
| 21 March 2014   | <ul style="list-style-type: none"><li>- The study sample size was increased by 10% (from 2,800 to 3,080 patients) following a written recommendation from the Steering Committee</li><li>- Addition of check mark for liver profile at screening in the schedule of assessments</li><li>- Clarification of the non requirement for patients who withdraw from active study participation but consent to minimal follow up (e.g., annual telephone follow up) to sign a separate ICF</li><li>- Treatments that are listed as "prohibited" were listed as "strongly discouraged" instead</li><li>- Clear definition of the differences between (i) discontinuing study drug, (ii) discontinuing active study participation, and (iii) completely withdrawing from the study</li><li>- Inclusion of additional detail to the End of Study section including description of the Common Study End Date</li><li>- Inclusion of a clear indication about which assessments are required at the yearly visits for patients who have discontinued randomized treatment</li><li>- Clarification about the collection requirement limited to SAEs and CV events in patients on non-randomized treatment; AEs and AESIs do not need to be collected in these patients unless they are receiving TCZ</li><li>- Clarification about the fact that fully diluted Tocilizumab solutions for infusion are only stable at room temperature for a maximum of 6 hours</li><li>- Volume of infusion determined by the current body weight, obtained at each visit prior to TCZ administration, rather than the last recorded body weight</li><li>- Inclusion into the schedule of assessments of the following statement: subjects must have Swollen joint count (SJC) <math>\geq 8</math> (66 joint count) and tender joint count (TJC) <math>\geq 8</math> (68 joint count) during screening or at the baseline visit for enrollment</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported