



## Clinical trial results:

### AspECT - A phase III, randomised study of aspirin and esomeprazole chemoprevention in Barrett's metaplasia & oesophagitis.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2004-003836-77 |
| Trial protocol           | GB             |
| Global end of trial date | 10 August 2017 |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 26 August 2018  |
| First version publication date    | 26 August 2018  |
| Summary attachment (see zip file) | AspECT_PrimaryPublication_Lancet_04Aug2018<br>(AspECT_PrimaryResults_Lancet_PIIS0140673618313886.pdf) |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | OCTO-003 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN85156844 |
| ClinicalTrials.gov id (NCT number) | NCT00357682    |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Oxford   |
| Sponsor organisation address | Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, OX4 2PG                                      |
| Public contact               | AspECT Trial Office, Oncology Clinical Trials Unit, University of Oxford, +44 1865 617331, enquiries@oncology.ox.ac.uk |
| Scientific contact           | AspECT Trial Office, Oncology Clinical Trials Unit, University of Oxford, +44 1865 617331, enquiries@oncology.ox.ac.uk |

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:

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**Results analysis stage**

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|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 31 May 2017    |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 31 May 2017    |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 10 August 2017 |
| Was the trial ended prematurely?                     | No             |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess whether intervention with aspirin results in a decreased all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia.

To assess whether high dose PPI therapy decreases the all causes of mortality or conversion rate from Barrett's Metaplasia to adenocarcinoma or high grade dysplasia.

Protection of trial subjects:

A data safety monitoring committee was established to review the data at regular intervals and ensure the safety of the trial patients.

Patient information sheets were provided to subjects prior to randomisation. Nurses and consultants also detailed to the patients the option to withdraw from the trial treatment and follow up at any point throughout the trial.

Patients were also provided with contact details of the clinical trial office and were encouraged to reach out if they had any questions at any time.

All adverse events throughout the trial were reported immediately to the trial office and reviewed if deemed serious.

Background therapy:

Proton Pump Inhibitors (PPI) are used in to reduce acid in patients experiencing reflux from the stomach.

Aspirin is a drug mainly used to treat pain, fever, or inflammation.

Evidence for comparator:

It has yet to be determined whether high or low dose PPI is optimal in treating acid reflux and potentially reducing oesophageal cancer.

Long term daily use of aspirin has been seen to reduce the risk of a number of cancers, most notably colon cancer. It is yet unknown for sure if this is the case in oesophageal cancer.

|   |  |
|---|--|
| Actual start date of recruitment                          | 04 March 2005  |
| Long term follow-up planned                               | Yes  |
| Long term follow-up rationale                             | Efficacy, Ethical reason, Regulatory reason, Scientific research, Safety |
| Long term follow-up duration                              | 10 Years   |
| Independent data monitoring committee (IDMC) involvement? | Yes  |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                      |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | United Kingdom: 2491 |
|--------------------------------------|----------------------|

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Canada: 44 |
| Worldwide total number of subjects   | 2535       |
| EEA total number of subjects         | 2491       |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1836 |
| From 65 to 84 years                       | 693  |
| 85 years and over                         | 6    |

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants were recruited from 4th March 2005 to 25th February 2009 in 86 centres in the United Kingdom and 1 centre in Canada. Participants were recruited by gastroenterologists and upper gastrointestinal surgeons at hospitals through clinics and endoscopy lists, including new and existing BE diagnoses.

### Pre-assignment

Screening details:

At least 5,726 patients were screened in 87 sites. Of the 5,726 screening records, 2,582 (2083 not meeting exclusion and 499 other reasons) were excluded based on trial exclusion reasons (contraindication to study drug, outside age range etc). Of the 3,100 remaining, 587 declined participation in the trial, leaving 2,557 total patients randomised

### Period 1

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

Blinding implementation details:

No blinding was performed

### Arms

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

Arm description:

Low Dose PPI (20mg daily)

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Esomeprazole      |
| Investigational medicinal product code | D9612000000       |
| Other name                             | Nexium            |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

20mg/day

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

Arm description:

High Dose PPI (80mg daily)

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Esomeprazole      |
| Investigational medicinal product code | D9612000000       |
| Other name                             | Nexium            |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

40mg/twice daily

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

Arm description:

Low Dose PPI (20mg daily) & Aspirin (300mg daily)

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |              |
|--|--------------|
| Investigational medicinal product name | Esomeprazole |
| Investigational medicinal product code | D9612000000  |
| Other name                             | Nexium       |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

20mg/day

|  |          |
|--|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

300mg/day

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

Arm description:

High Dose PPI (80mg daily) & Aspirin (300mg daily)

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Esomeprazole      |
| Investigational medicinal product code | D9612000000       |
| Other name                             | Nexium            |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

40mg/twice daily

|  |          |
|--|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

300mg/day

| <b>Number of subjects in period 1</b> | Arm A | Arm B | Arm C |
|---------------------------------------|-------|-------|-------|
| Started                               | 699   | 698   | 566   |
| Completed                             | 699   | 698   | 566   |

| <b>Number of subjects in period 1</b> | Arm D |
|---------------------------------------|-------|
| Started                               | 572   |
| Completed                             | 572   |

## Baseline characteristics

### Reporting groups

|  |       |
|--|-------|
| Reporting group title                              | Arm A |
| Reporting group description:                       |       |
| Low Dose PPI (20mg daily)                          |       |
| Reporting group title                              | Arm B |
| Reporting group description:                       |       |
| High Dose PPI (80mg daily)                         |       |
| Reporting group title                              | Arm C |
| Reporting group description:                       |       |
| Low Dose PPI (20mg daily) & Aspirin (300mg daily)  |       |
| Reporting group title                              | Arm D |
| Reporting group description:                       |       |
| High Dose PPI (80mg daily) & Aspirin (300mg daily) |       |

| Reporting group values   | Arm A    | Arm B    | Arm C    |
|--|----------|----------|----------|
| Number of subjects   | 699      | 698      | 566      |
| 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)   | 495      | 494      | 429      |
| From 65-84 years   | 202      | 204      | 134      |
| 85 years and over  | 2        | 0        | 3        |
| Age continuous   |          |          |          |
| Continuous age statistics by treatment arm and primary trial comparisons |          |          |          |
| Units: years   |          |          |          |
| median   | 59       | 59       | 58       |
| inter-quartile range (Q1-Q3)   | 51 to 65 | 51 to 66 | 50 to 64 |
| Gender categorical   |          |          |          |
| Gender characteristics by treatment arm and primary trial comparisons    |          |          |          |
| Units: Subjects  |          |          |          |
| Female   | 135      | 136      | 118      |
| Male   | 564      | 562      | 448      |

| Reporting group values                             | Arm D | Total |  |
|--|-------|-------|--|
| Number of subjects                                 | 572   | 2535  |  |
| Age categorical                                    |       |       |  |
| Units: Subjects                                    |       |       |  |
| In utero   | 0     | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     | 0     |  |
| Newborns (0-27 days)                               | 0     | 0     |  |

|  |          |      |  |
|--|----------|------|--|
| Infants and toddlers (28 days-23 months)                                 | 0        | 0    |  |
| Children (2-11 years)  | 0        | 0    |  |
| Adolescents (12-17 years)  | 0        | 0    |  |
| Adults (18-64 years)   | 418      | 1836 |  |
| From 65-84 years   | 153      | 693  |  |
| 85 years and over  | 1        | 6    |  |
| Age continuous   |          |      |  |
| Continuous age statistics by treatment arm and primary trial comparisons |          |      |  |
| Units: years   |          |      |  |
| median   | 58       |      |  |
| inter-quartile range (Q1-Q3)   | 50 to 65 | -    |  |
| Gender categorical   |          |      |  |
| Gender characteristics by treatment arm and primary trial comparisons    |          |      |  |
| Units: Subjects  |          |      |  |
| Female   | 124      | 513  |  |
| Male   | 448      | 2022 |  |

### Subject analysis sets

|  |                    |
|--|--------------------|
| Subject analysis set title                         | Aspirin            |
| Subject analysis set type                          | Intention-to-treat |
| Subject analysis set description:                  |                    |
| Patients randomised to receive 300mg daily aspirin |                    |
| Subject analysis set title                         | No Aspirin         |
| Subject analysis set type                          | Intention-to-treat |
| Subject analysis set description:                  |                    |
| Subjects randomised to receive no aspirin          |                    |
| Subject analysis set title                         | Low Dose PPI       |
| Subject analysis set type                          | Intention-to-treat |
| Subject analysis set description:                  |                    |
| Subjects randomised to receive 20mg daily PPI      |                    |
| Subject analysis set title                         | High Dose PPI      |
| Subject analysis set type                          | Intention-to-treat |
| Subject analysis set description:                  |                    |
| Subjects randomised to receive 80mg PPI daily      |                    |

| Reporting group values                             | Aspirin | No Aspirin | Low Dose PPI |
|--|---------|------------|--------------|
| Number of subjects                                 | 1138    | 1142       | 1265         |
| 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)                               | 847     | 854        | 924          |
| From 65-84 years                                   | 287     | 287        | 336          |
| 85 years and over                                  | 4       | 1          | 5            |

|  |          |          |          |
|--|----------|----------|----------|
| Age continuous   |          |          |          |
| Continuous age statistics by treatment arm and primary trial comparisons |          |          |          |
| Units: years   |          |          |          |
| median   | 58       | 58       | 59       |
| inter-quartile range (Q1-Q3)   | 50 to 65 | 50 to 65 | 51 to 65 |
| Gender categorical   |          |          |          |
| Gender characteristics by treatment arm and primary trial comparisons    |          |          |          |
| Units: Subjects  |          |          |          |
| Female   | 242      | 242      | 253      |
| Male   | 896      | 900      | 1012     |

|  |               |  |  |
|--|---------------|--|--|
| <b>Reporting group values</b>  | High Dose PPI |  |  |
| Number of subjects   | 1270          |  |  |
| Age categorical  |               |  |  |
| Units: Subjects  |               |  |  |
| In utero   | 0             |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                    | 0             |  |  |
| Newborns (0-27 days)   | 0             |  |  |
| Infants and toddlers (28 days-23<br>months)                              | 0             |  |  |
| Children (2-11 years)  | 0             |  |  |
| Adolescents (12-17 years)  | 0             |  |  |
| Adults (18-64 years)   | 912           |  |  |
| From 65-84 years   | 357           |  |  |
| 85 years and over  | 1             |  |  |
| Age continuous   |               |  |  |
| Continuous age statistics by treatment arm and primary trial comparisons |               |  |  |
| Units: years   |               |  |  |
| median   | 59            |  |  |
| inter-quartile range (Q1-Q3)   | 51 to 65      |  |  |
| Gender categorical   |               |  |  |
| Gender characteristics by treatment arm and primary trial comparisons    |               |  |  |
| Units: Subjects  |               |  |  |
| Female   | 260           |  |  |
| Male   | 1010          |  |  |



## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Arm A              |
| Reporting group description:<br>Low Dose PPI (20mg daily)                               |                    |
| Reporting group title   | Arm B              |
| Reporting group description:<br>High Dose PPI (80mg daily)                              |                    |
| Reporting group title   | Arm C              |
| Reporting group description:<br>Low Dose PPI (20mg daily) & Aspirin (300mg daily)       |                    |
| Reporting group title   | Arm D              |
| Reporting group description:<br>High Dose PPI (80mg daily) & Aspirin (300mg daily)      |                    |
| Subject analysis set title  | Aspirin            |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Patients randomised to receive 300mg daily aspirin |                    |
| Subject analysis set title  | No Aspirin         |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Subjects randomised to receive no aspirin          |                    |
| Subject analysis set title  | Low Dose PPI       |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Subjects randomised to receive 20mg daily PPI      |                    |
| Subject analysis set title  | High Dose PPI      |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Subjects randomised to receive 80mg PPI daily      |                    |

### Primary: First event of death, oesophageal adenocarcinoma, high grade dysplasia

|   |  |
|---|--|
| End point title   | First event of death, oesophageal adenocarcinoma, high grade dysplasia |
| End point description:<br>Death is recorded on a continuous basis through reporting from trial sites.<br><br>Oesophageal adenocarcinoma is recorded through endoscopies taken every two years or ad-hoc at clinician decision<br><br>High Grade Dysplasia is recorded through endoscopies taken every two years or ad-hoc at clinician decision |  |
| End point type  | Primary  |
| End point timeframe:<br>Events are assessed from the date of randomisation to the end of study which can be patient withdrawal, loss to follow up or study end (8 years or 10 years from randomisation, depending on consent)   |  |

| End point values            | Arm A           | Arm B           | Arm C           | Arm D           |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 699             | 698             | 566             | 572             |
| Units: 20                   | 99              | 87              | 75              | 52              |

| End point values            | Aspirin              | No Aspirin           | Low Dose PPI         | High Dose PPI        |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1138                 | 1142                 | 1265                 | 1270                 |
| Units: 20                   | 127                  | 154                  | 174                  | 139                  |

## Statistical analyses

| Statistical analysis title   | Primary Analysis (PPI)       |
|--|------------------------------|
| Statistical analysis description:  |                              |
| Accelerated Failure Time (AFT) analysis comparing time to primary event in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group. |                              |
| Comparison groups  | Low Dose PPI v High Dose PPI |
| Number of subjects included in analysis  | 2535                         |
| Analysis specification   | Pre-specified                |
| Analysis type  | superiority <sup>[1]</sup>   |
| P-value  | = 0.068                      |
| Method   | Accelerated Failure Time     |
| Parameter estimate   | Time Ratio                   |
| Point estimate   | 1.24                         |
| Confidence interval  |                              |
| level  | 95 %                         |
| sides  | 2-sided                      |
| lower limit  | 0.98                         |
| upper limit  | 1.57                         |

Notes:

[1] - 5% significance level is considered statistically significant

| Statistical analysis title  | Primary Analysis (Aspirin) |
|---|----------------------------|
| Statistical analysis description:   |                            |
| Accelerated Failure Time (AFT) analysis comparing time to primary event in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group. |                            |
| Comparison groups   | No Aspirin v Aspirin       |
| Number of subjects included in analysis   | 2280                       |
| Analysis specification  | Pre-specified              |
| Analysis type   | superiority                |
| P-value   | = 0.037                    |
| Method  | Accelerated Failure Time   |
| Parameter estimate  | Time Ratio                 |
| Point estimate  | 1.27                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.01    |
| upper limit         | 1.58    |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Secondary Analysis (PPI All cause mortality) |
|-----------------------------------|--|

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to all cause mortality in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

|   |                              |
|---|------------------------------|
| Comparison groups                       | Low Dose PPI v High Dose PPI |
| Number of subjects included in analysis | 2535                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.039                      |
| Method                                  | Accelerated Failure Time     |
| Parameter estimate                      | Time Ratio                   |
| Point estimate                          | 1.36                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 1.01                         |
| upper limit                             | 1.82                         |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Secondary Analysis (PPI Oesophageal Adenocarcinoma) |
|-----------------------------------|---|

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to oesophageal adenocarcinoma in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

|   |                              |
|---|------------------------------|
| Comparison groups                       | Low Dose PPI v High Dose PPI |
| Number of subjects included in analysis | 2535                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.864                      |
| Method                                  | Accelerated Failure Time     |
| Parameter estimate                      | Time Ratio                   |
| Point estimate                          | 1.04                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.67                         |
| upper limit                             | 1.61                         |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Secondary Analysis (High Grade Dysplasia) |
| Statistical analysis description:   |   |
| Accelerated Failure Time (AFT) analysis comparing time to high grade dysplasia in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group. |   |
| Comparison groups   | Low Dose PPI v High Dose PPI              |
| Number of subjects included in analysis   | 2535                                      |
| Analysis specification  | Pre-specified                             |
| Analysis type   | superiority                               |
| P-value   | = 0.119                                   |
| Method  | Accelerated Failure Time                  |
| Parameter estimate  | Time Ratio                                |
| Point estimate  | 1.36                                      |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 0.92                                      |
| upper limit   | 2.02                                      |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Secondary Analysis (Aspirin All Cause Mortality) |
| Statistical analysis description:   |  |
| Accelerated Failure Time (AFT) analysis comparing time to all cause mortality in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group. |  |
| Comparison groups   | Aspirin v No Aspirin                             |
| Number of subjects included in analysis   | 2280   |
| Analysis specification  | Pre-specified                                    |
| Analysis type   | superiority                                      |
| P-value   | = 0.159  |
| Method  | Accelerated Failure Time                         |
| Parameter estimate  | Time Ratio                                       |
| Point estimate  | 1.25   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.92   |
| upper limit   | 1.7  |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Secondary Analysis (Aspirin and oesophageal adeno) |
| Statistical analysis description:  |  |
| Accelerated Failure Time (AFT) analysis comparing time to oesophageal adenocarcinoma in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group. |  |
| Comparison groups  | Aspirin v No Aspirin                               |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 2280                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.921                  |
| Method                                  | Accelerated Failure Time |
| Parameter estimate                      | Time Ratio               |
| Point estimate                          | 1.02                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.64                     |
| upper limit                             | 1.64                     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Secondary Analysis (Aspirin High Grade Dysplasia) |
|-----------------------------------|---|

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to high grade dysplasia in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.

|   |                          |
|---|--------------------------|
| Comparison groups                       | Aspirin v No Aspirin     |
| Number of subjects included in analysis | 2280                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.053                  |
| Method                                  | Accelerated Failure Time |
| Parameter estimate                      | Time Ratio               |
| Point estimate                          | 1.51                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 1                        |
| upper limit                             | 2.29                     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Secondary Analysis (PPI Cause Specific Mortality) |
|-----------------------------------|---|

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to cause specific mortality in low dose PPI (20mg) patients to high dose PPI (80mg) patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and aspirin randomisation group.

Cause Specific Mortality: Death due to oesophageal adenocarcinoma

|   |                              |
|---|------------------------------|
| Comparison groups                       | Low Dose PPI v High Dose PPI |
| Number of subjects included in analysis | 2535                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.336                      |
| Method                                  | Accelerated Failure Time     |
| Parameter estimate                      | Time Ratio                   |
| Point estimate                          | 1.55                         |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.63    |
| upper limit         | 3.8     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Secondary Analysis (Aspirin Cause Specific Death) |
|-----------------------------------|---|

Statistical analysis description:

Accelerated Failure Time (AFT) analysis comparing time to cause specific mortality in aspirin patients to non-aspirin patients. Included in AFT model are stratification factors (Barrett's length, age group and presence of baseline intestinal metaplasia) and PPI randomisation group.

|   |                          |
|---|--------------------------|
| Comparison groups                       | Aspirin v No Aspirin     |
| Number of subjects included in analysis | 2280                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.983                  |
| Method                                  | Accelerated Failure Time |
| Parameter estimate                      | Time Ratio               |
| Point estimate                          | 1.01                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.38                     |
| upper limit                             | 2.69                     |

## Adverse events

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

Timeframe for reporting adverse events:

Adverse events were reported from the date of randomisation until 30 days after the end of treatment

Adverse event reporting additional description:

Adverse events were reported to the trial team by sites as soon as possible after the events occurred.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Low Dose PPI (20mg daily)

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

High Dose PPI (80mg daily)

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm C |
|-----------------------|-------|

Reporting group description:

Low Dose PPI (20mg daily) & Aspirin (300mg daily)

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm D |
|-----------------------|-------|

Reporting group description:

High Dose PPI (80mg daily) & Aspirin (300mg daily)

|                       |         |
|-----------------------|---------|
| Reporting group title | Aspirin |
|-----------------------|---------|

Reporting group description:

Patients randomised to 300mg daily aspirin treatment

|                       |            |
|-----------------------|------------|
| Reporting group title | No Aspirin |
|-----------------------|------------|

Reporting group description:

Patients randomised to received no aspirin treatment

|                       |              |
|-----------------------|--------------|
| Reporting group title | Low Dose PPI |
|-----------------------|--------------|

Reporting group description:

Patients randomised to 20mg daily PPI treatment

|                       |               |
|-----------------------|---------------|
| Reporting group title | High Dose PPI |
|-----------------------|---------------|

Reporting group description:

Patients randomised to 80mg daily PPI treatment

Notes:

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

Justification: The reason is that adverse events (non-serious) were only recorded if the event led to the patient withdrawing from study medication. Non serious AE details were not recorded.

| Serious adverse events  | Arm A              | Arm B              | Arm C              |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events                   |                    |                    |                    |
| subjects affected / exposed   | 183 / 699 (26.18%) | 195 / 698 (27.94%) | 176 / 566 (31.10%) |
| number of deaths (all causes)                                       | 48                 | 42                 | 46                 |
| number of deaths resulting from adverse events                      | 39                 | 33                 | 30                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                    |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Bile duct cancer                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder Cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| Brain cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           | 0 / 0           |
| Colorectal cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 6 / 699 (0.86%) | 4 / 698 (0.57%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 1           | 0 / 2           |
| Endometrial cancer                              |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gallbladder cancer                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric - Adenocarcinoma                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Laryngeal - Squamous cell carcinoma             |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukemia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| Liposarcoma                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Lung cancer                                     |                 |                 |                 |
| subjects affected / exposed                     | 5 / 699 (0.72%) | 7 / 698 (1.00%) | 7 / 566 (1.24%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 7           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 5           | 0 / 7           |
| Lymphoma  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 1           |
| Mesothelioma                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 0           |
| Metastatic cancer unknown origin                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 1           |
| Myeloma   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Neuroendocrine tumour                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal cancer                              |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 1           | 0 / 2           |
| Oral cancer                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 1           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 4 / 699 (0.57%) | 7 / 698 (1.00%) | 3 / 566 (0.53%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Renal cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 1           |
| Skin cancer melanoma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin cancer non-melanoma                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Testicular cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hematoma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ruptured aortic arch aneurism                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Thromboembolic event                            |                 |                 |                 |
| subjects affected / exposed                     | 5 / 699 (0.72%) | 7 / 698 (1.00%) | 6 / 566 (1.06%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 7           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Vasculitis                                      |                 |                 |                 |

|  |                 |                  |                 |
|--|-----------------|------------------|-----------------|
| subjects affected / exposed                          | 0 / 699 (0.00%) | 0 / 698 (0.00%)  | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Pregnancy, puerperium and perinatal conditions       |                 |                  |                 |
| Fetal death  |                 |                  |                 |
| subjects affected / exposed                          | 1 / 699 (0.14%) | 0 / 698 (0.00%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| General disorders and administration site conditions |                 |                  |                 |
| Fever  |                 |                  |                 |
| subjects affected / exposed                          | 0 / 699 (0.00%) | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Flu like symptoms                                    |                 |                  |                 |
| subjects affected / exposed                          | 0 / 699 (0.00%) | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Injection site reaction                              |                 |                  |                 |
| subjects affected / exposed                          | 1 / 699 (0.14%) | 0 / 698 (0.00%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Localized edema                                      |                 |                  |                 |
| subjects affected / exposed                          | 0 / 699 (0.00%) | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Non-cardiac chest pain                               |                 |                  |                 |
| subjects affected / exposed                          | 7 / 699 (1.00%) | 12 / 698 (1.72%) | 7 / 566 (1.24%) |
| occurrences causally related to treatment / all      | 0 / 7           | 0 / 13           | 0 / 7           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |
| Pain   |                 |                  |                 |
| subjects affected / exposed                          | 0 / 699 (0.00%) | 0 / 698 (0.00%)  | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Immune system disorders                         |                 |                 |                 |
| Allergic reaction                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaphylaxis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Autoimmune disorder                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Bronchial obstruction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchospasm                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 1 / 698 (0.14%) | 3 / 566 (0.53%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epistaxis                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 9 / 566 (1.59%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 7 / 9           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hiccups   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 3 / 698 (0.43%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tracheal stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wheezing  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusion                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mania   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychosis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Investigations                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Blood bilirubin increased                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| GGT increased                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Platelet count decreased                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitamin B12 deficiency                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Accidental death                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| Alcohol abuse                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 2 / 698 (0.29%) | 3 / 566 (0.53%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bruising  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cholecystectomy procedural complication         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 3 / 698 (0.43%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fracture  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 7 / 698 (1.00%) | 7 / 566 (1.24%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 7           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 6 / 699 (0.86%) | 4 / 698 (0.57%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 2 / 6           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intraoperative gastrointestinal injury          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Overdose  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative hemorrhage                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 3 / 566 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| Ruptured spleen                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound complication                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 4 / 698 (0.57%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic dissection                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve disease                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 699 (0.72%)  | 5 / 698 (0.72%)  | 6 / 566 (1.06%)  |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 9            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Atrial flutter                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 0 / 698 (0.00%)  | 1 / 566 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Atrioventricular block complete                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 1 / 698 (0.14%)  | 2 / 566 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac arrest                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 699 (0.29%)  | 1 / 698 (0.14%)  | 2 / 566 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            | 0 / 1            |
| Cardiomyopathy                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 699 (0.29%)  | 2 / 698 (0.29%)  | 0 / 566 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chest pain                                      |                  |                  |                  |
| subjects affected / exposed                     | 6 / 699 (0.86%)  | 9 / 698 (1.29%)  | 4 / 566 (0.71%)  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 12           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Heart failure                                   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 699 (0.57%)  | 1 / 698 (0.14%)  | 2 / 566 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myocardial infarction                           |                  |                  |                  |
| subjects affected / exposed                     | 12 / 699 (1.72%) | 12 / 698 (1.72%) | 11 / 566 (1.94%) |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 12           | 0 / 11           |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 3            | 0 / 3            |
| Pericardial effusion                            |                  |                  |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericarditis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Right ventricular dysfunction                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus bradycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus tachycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular arrhythmia                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amnesia   |                 |                 |                 |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Cognitive disturbance                           |                  |                 |                 |
| subjects affected / exposed                     | 4 / 699 (0.57%)  | 1 / 698 (0.14%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 1 / 4            | 1 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Dizziness                                       |                  |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Headache  |                  |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%)  | 5 / 698 (0.72%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 7           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Intracranial hemorrhage                         |                  |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%)  | 2 / 698 (0.29%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1           | 0 / 0           |
| Ischemia cerebrovascular                        |                  |                 |                 |
| subjects affected / exposed                     | 10 / 699 (1.43%) | 7 / 698 (1.00%) | 8 / 566 (1.41%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 7           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           | 0 / 0           |
| Memory impairment                               |                  |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%)  | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Motor neurone disease                           |                  |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Multiple system atrophy                         |                  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Parkinson's disease                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyramidal tract syndrome                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seizure   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Somnolence                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spasticity                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischemic attacks                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 699 (0.43%) | 5 / 698 (0.72%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vasovagal reaction                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 4 / 698 (0.57%) | 7 / 566 (1.24%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 7 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Febrile neutropenia                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spleen disorder                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vestibular disorder                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Retinal detachment                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Vitreous hemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal distension                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 3 / 698 (0.43%) | 7 / 566 (1.24%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 1 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ascites   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bloating  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cameron Ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colonic hemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colonic obstruction                             |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colonic perforation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 2 / 698 (0.29%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal hemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Enterocolitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal haemorrhage                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal obstruction                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal pain                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal varices haemorrhage                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophagitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrooesophageal reflux disease                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 5 / 698 (0.72%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal pain                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemorrhoidal hemorrhage                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemorrhoids                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileal obstruction                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic Colitis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mallory-Weiss tear                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 5 / 699 (0.72%) | 3 / 698 (0.43%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 3           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Alcoholic Hepatitis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bile duct stenosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bile duct stone                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 6 / 699 (0.86%) | 3 / 698 (0.43%) | 6 / 566 (1.06%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 4           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gallbladder necrosis                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Gallbladder pain                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gallbladder perforation                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 3 / 698 (0.43%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 4           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal calculi                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 699 (0.29%) | 1 / 698 (0.14%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal colic                                     |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 3 / 698 (0.43%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract obstruction                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |
| Goitre  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypothyroidism                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |  |
|---|-----------------|-----------------|-----------------|--|
| Avascular necrosis                              |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 1 / 566 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Cervical Spondylosis                            |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Hernia  |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 2 / 566 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Joint range of motion decreased cervical spine  |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Mortons neuroma                                 |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Muscle weakness lower limb                      |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Myalgia   |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |                 |  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteonecrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoporosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tendon rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anorectal infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Appendicitis perforated                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Biliary tract infection                         |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder infection                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bone infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Device related infection                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Enterocolitis infectious                        |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 6 / 698 (0.86%) | 5 / 566 (0.88%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye infection                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic infection                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inner Ear Infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal parasite                             |                 |                 |                 |

|   |                  |                  |                 |
|---|------------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 0 / 698 (0.00%)  | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Joint infection                                 |                  |                  |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%)  | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0           |
| Kidney infection                                |                  |                  |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%)  | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Lung infection                                  |                  |                  |                 |
| subjects affected / exposed                     | 19 / 699 (2.72%) | 12 / 698 (1.72%) | 9 / 566 (1.59%) |
| occurrences causally related to treatment / all | 0 / 24           | 0 / 15           | 0 / 14          |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            | 0 / 1           |
| Pharyngitis                                     |                  |                  |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Prostate infection                              |                  |                  |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%)  | 0 / 698 (0.00%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Psoas abscess                                   |                  |                  |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 1 / 698 (0.14%)  | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Salivary gland infection                        |                  |                  |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%)  | 0 / 698 (0.00%)  | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0           |
| Scrotal infection                               |                  |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 7 / 699 (1.00%) | 7 / 698 (1.00%) | 2 / 566 (0.35%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 10          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Soft tissue infection                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tooth infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper respiratory infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 4 / 699 (0.57%) | 0 / 698 (0.00%) | 4 / 566 (0.71%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 699 (0.43%) | 3 / 698 (0.43%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Acidosis  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 699 (0.00%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 699 (0.29%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperuricemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypokalemia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 1 / 566 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypomagnesemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 699 (0.00%) | 2 / 698 (0.29%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatremia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 699 (0.14%) | 1 / 698 (0.14%) | 0 / 566 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| Serious adverse events             | Arm D | Aspirin | No Aspirin |
|------------------------------------|-------|---------|------------|
| Total subjects affected by serious |       |         |            |

|   |                    |                     |                     |
|---|--------------------|---------------------|---------------------|
| adverse events  |                    |                     |                     |
| subjects affected / exposed   | 164 / 572 (28.67%) | 340 / 1138 (29.88%) | 378 / 1142 (33.10%) |
| number of deaths (all causes)                                       | 27                 | 73                  | 90                  |
| number of deaths resulting from adverse events                      | 17                 | 47                  | 72                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                     |                     |
| Bile duct cancer  |                    |                     |                     |
| subjects affected / exposed   | 1 / 572 (0.17%)    | 1 / 1138 (0.09%)    | 0 / 1142 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 1               | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 1               | 0 / 0               |
| Bladder Cancer  |                    |                     |                     |
| subjects affected / exposed   | 2 / 572 (0.35%)    | 2 / 1138 (0.18%)    | 3 / 1142 (0.26%)    |
| occurrences causally related to treatment / all                     | 0 / 2              | 0 / 2               | 0 / 4               |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0               | 0 / 2               |
| Brain cancer  |                    |                     |                     |
| subjects affected / exposed   | 0 / 572 (0.00%)    | 0 / 1138 (0.00%)    | 1 / 1142 (0.09%)    |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 0               | 0 / 1               |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0               | 0 / 1               |
| Breast cancer   |                    |                     |                     |
| subjects affected / exposed   | 0 / 572 (0.00%)    | 0 / 1138 (0.00%)    | 2 / 1142 (0.18%)    |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 0               | 0 / 3               |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0               | 0 / 3               |
| Colorectal cancer   |                    |                     |                     |
| subjects affected / exposed   | 4 / 572 (0.70%)    | 6 / 1138 (0.53%)    | 10 / 1142 (0.88%)   |
| occurrences causally related to treatment / all                     | 0 / 4              | 0 / 6               | 0 / 12              |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 3               | 0 / 5               |
| Endometrial cancer  |                    |                     |                     |
| subjects affected / exposed   | 0 / 572 (0.00%)    | 0 / 1138 (0.00%)    | 2 / 1142 (0.18%)    |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 0               | 0 / 2               |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0               | 0 / 0               |
| Gallbladder cancer  |                    |                     |                     |
| subjects affected / exposed   | 1 / 572 (0.17%)    | 1 / 1138 (0.09%)    | 0 / 1142 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 1               | 0 / 0               |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 1               | 0 / 0               |
| Gastric - Adenocarcinoma  |                    |                     |                     |

|   |                 |                   |                   |
|---|-----------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1             | 0 / 0             |
| Laryngeal - Squamous cell carcinoma             |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Leukemia  |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 2             |
| Liposarcoma                                     |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 1             |
| Lung cancer                                     |                 |                   |                   |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 10 / 1138 (0.88%) | 12 / 1142 (1.05%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 13            | 0 / 12            |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 9             | 0 / 9             |
| Lymphoma  |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%)  | 3 / 1142 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2             | 0 / 2             |
| Mesothelioma                                    |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 3 / 1142 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 3             |
| Metastatic cancer unknown origin                |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1             | 0 / 2             |
| Myeloma   |                 |                   |                   |

|   |                 |                  |                   |
|---|-----------------|------------------|-------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            | 0 / 1             |
| Neuroendocrine tumour                           |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Oesophageal cancer                              |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 4 / 1142 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            | 0 / 4             |
| Oral cancer                                     |                 |                  |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Ovarian cancer                                  |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Pancreatic cancer                               |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 3             |
| Prostate cancer                                 |                 |                  |                   |
| subjects affected / exposed                     | 6 / 572 (1.05%) | 8 / 1138 (0.70%) | 11 / 1142 (0.96%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 9            | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1             |
| Renal cancer                                    |                 |                  |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%) | 4 / 1142 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 2             |
| Skin cancer melanoma                            |                 |                  |                   |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            | 0 / 0            |
| Skin cancer non-melanoma                        |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 0            |
| Testicular cancer                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Vascular disorders                              |                 |                  |                  |
| Hematoma  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypertension                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypotension                                     |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 3 / 1138 (0.26%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Peripheral ischaemia                            |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Ruptured aortic arch aneurism                   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            | 0 / 0            |
| Thromboembolic event                            |                 |                  |                  |



|  |                  |                   |                   |
|--|------------------|-------------------|-------------------|
| subjects affected / exposed                          | 4 / 572 (0.70%)  | 10 / 1138 (0.88%) | 12 / 1142 (1.05%) |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 10            | 0 / 12            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 2             |
| Vasculitis   |                  |                   |                   |
| subjects affected / exposed                          | 0 / 572 (0.00%)  | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| Pregnancy, puerperium and perinatal conditions       |                  |                   |                   |
| Fetal death  |                  |                   |                   |
| subjects affected / exposed                          | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| General disorders and administration site conditions |                  |                   |                   |
| Fever  |                  |                   |                   |
| subjects affected / exposed                          | 1 / 572 (0.17%)  | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| Flu like symptoms                                    |                  |                   |                   |
| subjects affected / exposed                          | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| Injection site reaction                              |                  |                   |                   |
| subjects affected / exposed                          | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| Localized edema                                      |                  |                   |                   |
| subjects affected / exposed                          | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |
| Non-cardiac chest pain                               |                  |                   |                   |
| subjects affected / exposed                          | 12 / 572 (2.10%) | 19 / 1138 (1.67%) | 19 / 1142 (1.66%) |
| occurrences causally related to treatment / all      | 0 / 14           | 0 / 21            | 0 / 20            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0             |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| Pain  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Immune system disorders                         |                 |                  |                  |
| Allergic reaction                               |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Anaphylaxis                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Autoimmune disorder                             |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Respiratory, thoracic and mediastinal disorders |                 |                  |                  |
| Bronchial obstruction                           |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Bronchospasm                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Chronic obstructive pulmonary disease           |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Dyspnoea  |                 |                  |                  |

|   |                 |                   |                  |
|---|-----------------|-------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 3 / 1138 (0.26%)  | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Epistaxis                                       |                 |                   |                  |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 13 / 1138 (1.14%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 4 / 4           | 11 / 13           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Hiccups   |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Pleural effusion                                |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Pneumothorax                                    |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Pulmonary oedema                                |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Pulmonary fibrosis                              |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Respiratory failure                             |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Tracheal stenosis                               |                 |                   |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Wheezing  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Psychiatric disorders                           |                 |                  |                  |
| Anxiety   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Confusion                                       |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Delirium  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Depression                                      |                 |                  |                  |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 4 / 1138 (0.35%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Mania   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Psychosis                                       |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Suicide attempt                                 |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                           | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all            | 0 / 1           | 0 / 1            | 0 / 1            |
| <b>Investigations</b>                                 |                 |                  |                  |
| Blood bilirubin increased                             |                 |                  |                  |
| subjects affected / exposed                           | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 0            |
| GGT increased   |                 |                  |                  |
| subjects affected / exposed                           | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 0            |
| Platelet count decreased                              |                 |                  |                  |
| subjects affected / exposed                           | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 0            |
| Vitamin B12 deficiency                                |                 |                  |                  |
| subjects affected / exposed                           | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 0            |
| <b>Injury, poisoning and procedural complications</b> |                 |                  |                  |
| Accidental death                                      |                 |                  |                  |
| subjects affected / exposed                           | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 2            |
| Alcohol abuse   |                 |                  |                  |
| subjects affected / exposed                           | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all            | 0 / 1           | 0 / 1            | 0 / 0            |
| Ankle fracture  |                 |                  |                  |
| subjects affected / exposed                           | 1 / 572 (0.17%) | 4 / 1138 (0.35%) | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 4            | 0 / 4            |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0            | 0 / 0            |

|   |                 |                   |                   |
|---|-----------------|-------------------|-------------------|
| Bruising  |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Cholecystectomy procedural complication         |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Fall  |                 |                   |                   |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 7 / 1138 (0.62%)  | 4 / 1142 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 8             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1             | 0 / 0             |
| Fracture  |                 |                   |                   |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 11 / 1138 (0.97%) | 9 / 1142 (0.79%)  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 12            | 0 / 9             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 1             |
| Head injury                                     |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Hip fracture                                    |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%)  | 10 / 1142 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3             | 2 / 11            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Intraoperative gastrointestinal injury          |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Joint dislocation                               |                 |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Overdose  |                 |                   |                   |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Postoperative hemorrhage                        |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 3 / 1138 (0.26%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2            | 0 / 0            |
| Ruptured spleen                                 |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Wound complication                              |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Wrist fracture                                  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Cardiac disorders                               |                 |                  |                  |
| Acute coronary syndrome                         |                 |                  |                  |
| subjects affected / exposed                     | 6 / 572 (1.05%) | 7 / 1138 (0.62%) | 6 / 1142 (0.53%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 7            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Aortic dissection                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Aortic stenosis                                 |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Aortic valve disease                            |                 |                  |                  |

|   |                 |                  |                   |
|---|-----------------|------------------|-------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Atrial fibrillation                             |                 |                  |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 8 / 1138 (0.70%) | 10 / 1142 (0.88%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 8            | 1 / 14            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Atrial flutter                                  |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Atrioventricular block complete                 |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Cardiac arrest                                  |                 |                  |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            | 0 / 3             |
| Cardiomyopathy                                  |                 |                  |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%) | 4 / 1142 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Chest pain                                      |                 |                  |                   |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 8 / 1138 (0.70%) | 15 / 1142 (1.31%) |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 8            | 0 / 18            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Heart failure                                   |                 |                  |                   |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 5 / 1138 (0.44%) | 5 / 1142 (0.44%)  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 6            | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0             |
| Myocardial infarction                           |                 |                  |                   |



|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 13 / 572 (2.27%) | 24 / 1138 (2.11%) | 24 / 1142 (2.10%) |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 24            | 0 / 24            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 5             | 0 / 7             |
| Pericardial effusion                            |                  |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%)  | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Pericarditis                                    |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Right ventricular dysfunction                   |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Sinus bradycardia                               |                  |                   |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%)  | 6 / 1138 (0.53%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Sinus tachycardia                               |                  |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%)  | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Supraventricular tachycardia                    |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Ventricular arrhythmia                          |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Ventricular tachycardia                         |                  |                   |                   |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%)  | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Nervous system disorders                        |                  |                   |                   |
| Amnesia   |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Cognitive disturbance                           |                  |                   |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%)  | 6 / 1138 (0.53%)  | 5 / 1142 (0.44%)  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 6             | 2 / 5             |
| deaths causally related to treatment / all      | 1 / 1            | 1 / 1             | 0 / 0             |
| Dizziness                                       |                  |                   |                   |
| subjects affected / exposed                     | 1 / 572 (0.17%)  | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Headache  |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 4 / 1138 (0.35%)  | 6 / 1142 (0.53%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5             | 0 / 8             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Intracranial hemorrhage                         |                  |                   |                   |
| subjects affected / exposed                     | 3 / 572 (0.52%)  | 5 / 1138 (0.44%)  | 5 / 1142 (0.44%)  |
| occurrences causally related to treatment / all | 3 / 3            | 4 / 5             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 3             |
| Ischemia cerebrovascular                        |                  |                   |                   |
| subjects affected / exposed                     | 10 / 572 (1.75%) | 18 / 1138 (1.58%) | 17 / 1142 (1.49%) |
| occurrences causally related to treatment / all | 1 / 13           | 1 / 21            | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| Memory impairment                               |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Motor neurone disease                           |                  |                   |                   |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Multiple system atrophy                         |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1            |
| Parkinson's disease                             |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Presyncope                                      |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Pyramidal tract syndrome                        |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Seizure   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Somnolence                                      |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Spasticity                                      |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Syncope   |                 |                  |                  |

|   |                 |                   |                  |
|---|-----------------|-------------------|------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%)  | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3             | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Transient ischemic attacks                      |                 |                   |                  |
| subjects affected / exposed                     | 6 / 572 (1.05%) | 10 / 1138 (0.88%) | 8 / 1142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 11            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Vasovagal reaction                              |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Blood and lymphatic system disorders            |                 |                   |                  |
| Anaemia   |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 8 / 1138 (0.70%)  | 6 / 1142 (0.53%) |
| occurrences causally related to treatment / all | 0 / 1           | 7 / 8             | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Febrile neutropenia                             |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Spleen disorder                                 |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Ear and labyrinth disorders                     |                 |                   |                  |
| Vertigo   |                 |                   |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 3 / 1138 (0.26%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Vestibular disorder                             |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Eye disorders                                   |                 |                   |                  |

|   |                 |                   |                  |
|---|-----------------|-------------------|------------------|
| Retinal detachment                              |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Vitreous hemorrhage                             |                 |                   |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 2             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Gastrointestinal disorders                      |                 |                   |                  |
| Abdominal distension                            |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Abdominal pain                                  |                 |                   |                  |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 10 / 1138 (0.88%) | 6 / 1142 (0.53%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 10            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Ascites   |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Bloating  |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Cameron Ulcer                                   |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Colitis   |                 |                   |                  |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 3 / 1138 (0.26%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 3             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Colonic hemorrhage                              |                 |                   |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Colonic obstruction                             |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Colonic perforation                             |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Constipation                                    |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Diverticulitis                                  |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 4 / 1138 (0.35%) | 5 / 1142 (0.44%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Duodenal hemorrhage                             |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Dyspepsia                                       |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Dysphagia                                       |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Enterocolitis                                   |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Oesophageal haemorrhage                         |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Oesophageal obstruction                         |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Oesophageal pain                                |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Oesophageal varices haemorrhage                 |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Oesophagitis                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Gastric haemorrhage                             |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 4 / 1138 (0.35%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 2 / 2           | 3 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1            |
| Gastritis                                       |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Gastrooesophageal reflux disease                |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 7 / 1142 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Gastrointestinal pain                           |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hemorrhoidal hemorrhage                         |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 3 / 1138 (0.26%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hemorrhoids                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Ileal obstruction                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Ileus   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Ischaemic Colitis                               |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Mallory-Weiss tear                              |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Pancreatitis                                    |                 |                  |                  |



|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 572 (0.87%) | 9 / 1138 (0.79%) | 8 / 1142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 9            | 0 / 13           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1            |
| Rectal haemorrhage                              |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Small intestinal obstruction                    |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Upper gastrointestinal haemorrhage              |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 4 / 1138 (0.35%) | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 2 / 2           | 3 / 4            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Vomiting  |                 |                  |                  |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 6 / 1138 (0.53%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 7            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hepatobiliary disorders                         |                 |                  |                  |
| Alcoholic Hepatitis                             |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Bile duct stenosis                              |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Bile duct stone                                 |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Cholecystitis                                   |                 |                  |                  |

|   |                 |                   |                  |
|---|-----------------|-------------------|------------------|
| subjects affected / exposed                     | 7 / 572 (1.22%) | 13 / 1138 (1.14%) | 9 / 1142 (0.79%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 15            | 0 / 10           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Gallbladder necrosis                            |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1             | 0 / 0            |
| Gallbladder pain                                |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Gallbladder perforation                         |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Hepatic failure                                 |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 4 / 1138 (0.35%)  | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4             | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4             | 0 / 2            |
| Skin and subcutaneous tissue disorders          |                 |                   |                  |
| Skin ulcer                                      |                 |                   |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Renal and urinary disorders                     |                 |                   |                  |
| Acute kidney injury                             |                 |                   |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 3 / 1138 (0.26%)  | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Chronic kidney disease                          |                 |                   |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%)  | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0            |
| Haematuria                                      |                 |                   |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%) | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Renal calculi                                   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 2 / 1138 (0.18%) | 3 / 1142 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Renal colic                                     |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Urinary retention                               |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 3 / 1138 (0.26%) | 5 / 1142 (0.44%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Urinary tract obstruction                       |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Endocrine disorders                             |                 |                  |                  |
| Goitre  |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypothyroidism                                  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Musculoskeletal and connective tissue disorders |                 |                  |                  |
| Arthralgia                                      |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| Arthritis                                       |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Avascular necrosis                              |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Back pain                                       |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Cervical Spondylosis                            |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hernia  |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 4 / 1138 (0.35%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Joint range of motion decreased cervical spine  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Mortons neuroma                                 |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Muscle weakness lower limb                      |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Myalgia   |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Neck pain                                       |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Osteonecrosis                                   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Osteoporosis                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 2 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Tendon rupture                                  |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Infections and infestations                     |                 |                  |                  |
| Abdominal infection                             |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Anorectal infection                             |                 |                  |                  |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Appendicitis                                    |                 |                  |                  |
| subjects affected / exposed                     | 3 / 572 (0.52%) | 3 / 1138 (0.26%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Appendicitis perforated                         |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Biliary tract infection                         |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Bladder infection                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Bone infection                                  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Device related infection                        |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Enterocolitis infectious                        |                 |                  |                  |
| subjects affected / exposed                     | 4 / 572 (0.70%) | 9 / 1138 (0.79%) | 9 / 1142 (0.79%) |
| occurrences causally related to treatment / all | 3 / 6           | 3 / 11           | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Eye infection                                   |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hepatic infection                               |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Inner Ear Infection                             |                 |                  |                  |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Intestinal parasite                             |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Joint infection                                 |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| Kidney infection                                |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Lung infection                                  |                  |                   |                   |
| subjects affected / exposed                     | 16 / 572 (2.80%) | 25 / 1138 (2.20%) | 31 / 1142 (2.71%) |
| occurrences causally related to treatment / all | 0 / 27           | 0 / 41            | 0 / 39            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3             | 0 / 3             |
| Pharyngitis                                     |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Prostate infection                              |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Psoas abscess                                   |                  |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%)  | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Salivary gland infection                        |                  |                   |                   |

|   |                 |                   |                   |
|---|-----------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Scrotal infection                               |                 |                   |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Sepsis  |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 2 / 1142 (0.18%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Skin infection                                  |                 |                   |                   |
| subjects affected / exposed                     | 5 / 572 (0.87%) | 7 / 1138 (0.62%)  | 14 / 1142 (1.23%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 7             | 0 / 17            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Soft tissue infection                           |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Tooth infection                                 |                 |                   |                   |
| subjects affected / exposed                     | 2 / 572 (0.35%) | 2 / 1138 (0.18%)  | 0 / 1142 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Upper respiratory infection                     |                 |                   |                   |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%)  | 1 / 1142 (0.09%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Urinary tract infection                         |                 |                   |                   |
| subjects affected / exposed                     | 7 / 572 (1.22%) | 11 / 1138 (0.97%) | 4 / 1142 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 12            | 0 / 4             |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1             | 0 / 0             |
| Wound infection                                 |                 |                   |                   |



|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 1 / 1138 (0.09%) | 6 / 1142 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Metabolism and nutrition disorders              |                 |                  |                  |
| Acidosis  |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hyperglycemia                                   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 4 / 1142 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hyperkalemia                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hyperuricemia                                   |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypoglycemia                                    |                 |                  |                  |
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 1 / 1142 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypokalemia                                     |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 2 / 1138 (0.18%) | 0 / 1142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hypomagnesemia                                  |                 |                  |                  |
| subjects affected / exposed                     | 1 / 572 (0.17%) | 1 / 1138 (0.09%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1            | 3 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Hyponatremia                                    |                 |                  |                  |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 2 / 1142 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |

| <b>Serious adverse events</b>                                       | Low Dose PPI        | High Dose PPI       |  |
|---|---------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                     |                     |  |
| subjects affected / exposed   | 359 / 1265 (28.38%) | 359 / 1270 (28.27%) |  |
| number of deaths (all causes)                                       | 94                  | 69                  |  |
| number of deaths resulting from adverse events                      | 69                  | 50                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                     |  |
| Bile duct cancer  |                     |                     |  |
| subjects affected / exposed   | 0 / 1265 (0.00%)    | 1 / 1270 (0.08%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 1               |  |
| Bladder Cancer  |                     |                     |  |
| subjects affected / exposed   | 1 / 1265 (0.08%)    | 4 / 1270 (0.31%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 5               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 2               |  |
| Brain cancer  |                     |                     |  |
| subjects affected / exposed   | 0 / 1265 (0.00%)    | 1 / 1270 (0.08%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 1               |  |
| Breast cancer   |                     |                     |  |
| subjects affected / exposed   | 1 / 1265 (0.08%)    | 1 / 1270 (0.08%)    |  |
| occurrences causally related to treatment / all                     | 0 / 2               | 0 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 2               | 0 / 1               |  |
| Colorectal cancer   |                     |                     |  |
| subjects affected / exposed   | 8 / 1265 (0.63%)    | 8 / 1270 (0.63%)    |  |
| occurrences causally related to treatment / all                     | 0 / 9               | 0 / 9               |  |
| deaths causally related to treatment / all                          | 0 / 6               | 0 / 2               |  |
| Endometrial cancer  |                     |                     |  |
| subjects affected / exposed   | 2 / 1265 (0.16%)    | 0 / 1270 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 2               | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Gallbladder cancer                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Gastric - Adenocarcinoma                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Laryngeal - Squamous cell carcinoma             |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Leukemia  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| Liposarcoma                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Lung cancer                                     |                   |                   |  |
| subjects affected / exposed                     | 12 / 1265 (0.95%) | 10 / 1270 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 7             |  |
| Lymphoma  |                   |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1             |  |
| Mesothelioma                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| Metastatic cancer unknown origin                |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2             |  |
| Myeloma   |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1             |  |
| Neuroendocrine tumour                           |                  |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Oesophageal cancer                              |                  |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 1             |  |
| Oral cancer                                     |                  |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ovarian cancer                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pancreatic cancer                               |                  |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2             |  |
| Prostate cancer                                 |                  |                   |  |
| subjects affected / exposed                     | 6 / 1265 (0.47%) | 13 / 1270 (1.02%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Renal cancer                                    |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            |  |
| Skin cancer melanoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Skin cancer non-melanoma                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Testicular cancer                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Hematoma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypotension                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ruptured aortic arch aneurism                   |                  |                  |  |

|  |                   |                   |  |
|--|-------------------|-------------------|--|
| subjects affected / exposed                          | 1 / 1265 (0.08%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 1             | 0 / 1             |  |
| Thromboembolic event                                 |                   |                   |  |
| subjects affected / exposed                          | 11 / 1265 (0.87%) | 11 / 1270 (0.87%) |  |
| occurrences causally related to treatment / all      | 0 / 11            | 0 / 11            |  |
| deaths causally related to treatment / all           | 0 / 1             | 0 / 1             |  |
| Vasculitis   |                   |                   |  |
| subjects affected / exposed                          | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Pregnancy, puerperium and perinatal conditions       |                   |                   |  |
| Fetal death  |                   |                   |  |
| subjects affected / exposed                          | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| General disorders and administration site conditions |                   |                   |  |
| Fever  |                   |                   |  |
| subjects affected / exposed                          | 0 / 1265 (0.00%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Flu like symptoms                                    |                   |                   |  |
| subjects affected / exposed                          | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Injection site reaction                              |                   |                   |  |
| subjects affected / exposed                          | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Localized edema                                      |                   |                   |  |
| subjects affected / exposed                          | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Non-cardiac chest pain                          |                   |                   |  |
| subjects affected / exposed                     | 14 / 1265 (1.11%) | 24 / 1270 (1.89%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 27            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pain  |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Immune system disorders                         |                   |                   |  |
| Allergic reaction                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anaphylaxis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Autoimmune disorder                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Bronchial obstruction                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (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                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Dyspnoea  |                   |                  |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Epistaxis                                       |                   |                  |  |
| subjects affected / exposed                     | 11 / 1265 (0.87%) | 4 / 1270 (0.31%) |  |
| occurrences causally related to treatment / all | 7 / 11            | 4 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hiccups   |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pleural effusion                                |                   |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pneumothorax                                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary oedema                                |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary fibrosis                              |                   |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Respiratory failure                             |                   |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 4 / 1270 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheal stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wheezing  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Anxiety   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Confusion                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (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                     | 0 / 1265 (0.00%) | 6 / 1270 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mania   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychosis                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Investigations                                  |                  |                  |  |
| Blood bilirubin increased                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| GGT increased                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Platelet count decreased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitamin B12 deficiency                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Accidental death                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Alcohol abuse                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Ankle fracture                                  |                  |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bruising  |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cholecystectomy procedural complication         |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fall  |                  |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 6 / 1270 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Fracture  |                  |                   |  |
| subjects affected / exposed                     | 9 / 1265 (0.71%) | 11 / 1270 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Head injury                                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (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                     | 8 / 1265 (0.63%) | 5 / 1270 (0.39%)  |  |
| occurrences causally related to treatment / all | 2 / 8            | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intraoperative gastrointestinal injury          |                  |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Joint dislocation                               |                  |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Overdose  |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Postoperative hemorrhage                        |                  |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0             |  |
| Ruptured spleen                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Wound complication                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Wrist fracture                                  |                  |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiac disorders                               |                  |                   |  |
| Acute coronary syndrome                         |                  |                   |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 10 / 1270 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aortic dissection                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aortic stenosis                                 |                  |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Aortic valve disease                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial fibrillation                             |                   |                   |  |
| subjects affected / exposed                     | 11 / 1265 (0.87%) | 7 / 1270 (0.55%)  |  |
| occurrences causally related to treatment / all | 0 / 11            | 1 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial flutter                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1             |  |
| Cardiomyopathy                                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 4 / 1270 (0.31%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chest pain                                      |                   |                   |  |
| subjects affected / exposed                     | 10 / 1265 (0.79%) | 13 / 1270 (1.02%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 1 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Heart failure                                   |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 6 / 1265 (0.47%)  | 4 / 1270 (0.31%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myocardial infarction                           |                   |                   |  |
| subjects affected / exposed                     | 23 / 1265 (1.82%) | 25 / 1270 (1.97%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 25            |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 5             |  |
| Pericardial effusion                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pericarditis                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Right ventricular dysfunction                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sinus bradycardia                               |                   |                   |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%)  | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sinus tachycardia                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Supraventricular tachycardia                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Ventricular arrhythmia                          |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Ventricular tachycardia                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Nervous system disorders                        |                   |                   |  |
| Amnesia   |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cognitive disturbance                           |                   |                   |  |
| subjects affected / exposed                     | 8 / 1265 (0.63%)  | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 1 / 8             | 2 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 1 / 1             |  |
| Dizziness                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Headache  |                   |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%)  | 5 / 1270 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Intracranial hemorrhage                         |                   |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%)  | 5 / 1270 (0.39%)  |  |
| occurrences causally related to treatment / all | 1 / 5             | 3 / 5             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Ischemia cerebrovascular                        |                   |                   |  |
| subjects affected / exposed                     | 18 / 1265 (1.42%) | 17 / 1270 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 1 / 20            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Memory impairment                               |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Motor neurone disease                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple system atrophy                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Parkinson's disease                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyramidal tract syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Somnolence                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spasticity                                      |                  |                  |  |



|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Syncope   |                  |                   |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Transient ischemic attacks                      |                  |                   |  |
| subjects affected / exposed                     | 7 / 1265 (0.55%) | 11 / 1270 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Vasovagal reaction                              |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Blood and lymphatic system disorders            |                  |                   |  |
| Anaemia   |                  |                   |  |
| subjects affected / exposed                     | 9 / 1265 (0.71%) | 5 / 1270 (0.39%)  |  |
| occurrences causally related to treatment / all | 7 / 9            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Febrile neutropenia                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Spleen disorder                                 |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ear and labyrinth disorders                     |                  |                   |  |
| Vertigo   |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Vestibular disorder                             |                  |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Eye disorders                                   |                   |                  |  |
| Retinal detachment                              |                   |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vitreous hemorrhage                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Gastrointestinal disorders                      |                   |                  |  |
| Abdominal distension                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Abdominal pain                                  |                   |                  |  |
| subjects affected / exposed                     | 10 / 1265 (0.79%) | 6 / 1270 (0.47%) |  |
| occurrences causally related to treatment / all | 1 / 10            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ascites   |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bloating  |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cameron Ulcer                                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Colitis   |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colonic hemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colonic obstruction                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colonic perforation                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 1265 (0.40%) | 4 / 1270 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal hemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysphagia                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal haemorrhage                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal obstruction                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal pain                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal varices haemorrhage                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 6 / 1270 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal pain                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hemorrhoidal hemorrhage                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hemorrhoids                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileal obstruction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic Colitis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mallory-Weiss tear                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 9 / 1265 (0.71%) | 8 / 1270 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 4 / 1270 (0.31%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 2 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 5 / 1270 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Alcoholic Hepatitis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stenosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stone                                 |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cholecystitis                                   |                   |                   |  |
| subjects affected / exposed                     | 12 / 1265 (0.95%) | 10 / 1270 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gallbladder necrosis                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Gallbladder pain                                |                   |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gallbladder perforation                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hepatic failure                                 |                   |                   |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%)  | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 2             |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Skin ulcer                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal and urinary disorders                     |                   |                   |  |
| Acute kidney injury                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%)  | 4 / 1270 (0.31%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic kidney disease                          |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal calculi                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 5 / 1270 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract obstruction                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Goitre  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypothyroidism                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 1265 (0.24%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Avascular necrosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical Spondylosis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hernia  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint range of motion decreased cervical spine  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mortons neuroma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle weakness lower limb                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myalgia   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neck pain                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteonecrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteoporosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anorectal infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 2 / 1270 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 5 / 1270 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Appendicitis perforated                         |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Biliary tract infection                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bladder infection                               |                  |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bone infection                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Device related infection                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Enterocolitis infectious                        |                  |                   |  |
| subjects affected / exposed                     | 8 / 1265 (0.63%) | 10 / 1270 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 3 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Eye infection                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hepatic infection                               |                  |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Inner Ear Infection                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Intestinal parasite                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Joint infection                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Kidney infection                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lung infection                                  |                   |                   |  |
| subjects affected / exposed                     | 28 / 1265 (2.21%) | 28 / 1270 (2.20%) |  |
| occurrences causally related to treatment / all | 0 / 38            | 0 / 42            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 2             |  |
| Pharyngitis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%)  | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Prostate infection                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%)  | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Psoas abscess                                   |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Salivary gland infection                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Scrotal infection                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 3 / 1270 (0.24%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sepsis  |                  |                   |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Skin infection                                  |                  |                   |  |
| subjects affected / exposed                     | 9 / 1265 (0.71%) | 12 / 1270 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Soft tissue infection                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Tooth infection                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 2 / 1270 (0.16%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Upper respiratory infection                     |                  |                   |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Urinary tract infection                         |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 1265 (0.63%) | 7 / 1270 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Wound infection                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 1265 (0.32%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Acidosis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycemia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1265 (0.16%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkalemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperuricemia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 0 / 1270 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalemia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypomagnesemia                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1265 (0.00%) | 3 / 1270 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 4 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatremia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1265 (0.08%) | 1 / 1270 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Arm A           | Arm B           | Arm C           |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |
| subjects affected / exposed                           | 0 / 699 (0.00%) | 0 / 698 (0.00%) | 0 / 566 (0.00%) |

| <b>Non-serious adverse events</b>                     | Arm D           | Aspirin          | No Aspirin       |
|---|-----------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                 |                  |                  |
| subjects affected / exposed                           | 0 / 572 (0.00%) | 0 / 1138 (0.00%) | 0 / 1142 (0.00%) |

| <b>Non-serious adverse events</b>                     | Low Dose PPI     | High Dose PPI    |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 0 / 1265 (0.00%) | 0 / 1270 (0.00%) |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 01 September 2004 | Note that amendments to add sites or change Principal Investigators at active sites have not been listed here. |
| 10 September 2004 | Changes to GP letter, PIS and Patient Study Card   |
| 01 November 2004  | Changes to MREC form, ICF, recruitment flow chart, PIS, GP letter and Patient Study Card                       |
| 01 February 2005  | Changes to ICF, PIS and Patient Study Card   |
| 23 March 2005     | Drug Distribution  |
| 27 July 2005      | Protocol_V5 & PIS_V6 Update  |
| 17 August 2005    | Change of Sponsor from Leicester to Oxford   |
| 20 January 2006   | Protocol_V6 & Supporting Doc   |
| 17 July 2006      | Poster   |
| 19 January 2007   | Drug labelling   |
| 05 February 2007  | Protocol_V7 & Supporting Docs  |
| 09 July 2007      | Poster   |
| 22 August 2007    | Protocol_V8  |
| 25 September 2007 | Protocol_V9 & Supporting Documents   |
| 04 April 2008     | Drug labelling   |
| 01 September 2008 | Appointment of joint CI  |
| 10 September 2008 | Recruitment extension  |
| 23 October 2009   | Drug distribution in Northern Ireland  |
| 31 March 2010     | Letter for patients with overdue endoscopy   |
| 30 July 2010      | Protocol_V10 & Supporting Documents  |
| 02 February 2011  | Patient Newsletter   |



|                 |                                       |
|-----------------|---------------------------------------|
| 09 May 2014     | End of trial PIS and GP letter        |
| 20 January 2015 | Protocol_V11.0 & Supporting_Documents |
| 26 January 2016 | Protocol_V12.0 & Supporting Documents |
| 23 March 2016   | Patient Newsletter & PIS V14.0        |
| 05 April 2016   | Drug labelling                        |
| 14 June 2017    | EndOfTrial_PatientLetter              |

Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported

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### **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/30057104>