



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2014-000770-19          |
| Trial protocol           | CZ SK HU DE ES BG PL RO |
| Global end of trial date | 04 October 2018         |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 15 January 2020 |
| First version publication date | 31 October 2019 |
| Version creation reason        |                 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D5740C00001 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02174627 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | AstraZeneca                                                                                   |
| Sponsor organisation address | 101 Orchard Ridge Drive, Gaithersburg, Maryland, United States, 20878                         |
| Public contact               | Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 04 October 2018 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 04 October 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of roxadustat compared with placebo for the treatment of anemia in chronic kidney disease (CKD) participants not on dialysis.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Sample.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 26 June 2014 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 74           |
| Country: Number of subjects enrolled | Brazil: 85              |
| Country: Number of subjects enrolled | Bulgaria: 78            |
| Country: Number of subjects enrolled | Canada: 50              |
| Country: Number of subjects enrolled | Colombia: 4             |
| Country: Number of subjects enrolled | Czech Republic: 20      |
| Country: Number of subjects enrolled | Germany: 5              |
| Country: Number of subjects enrolled | Hungary: 50             |
| Country: Number of subjects enrolled | India: 205              |
| Country: Number of subjects enrolled | Korea, Republic of: 245 |
| Country: Number of subjects enrolled | Malaysia: 15            |
| Country: Number of subjects enrolled | Mexico: 101             |
| Country: Number of subjects enrolled | Peru: 147               |
| Country: Number of subjects enrolled | Philippines: 97         |
| Country: Number of subjects enrolled | Poland: 38              |
| Country: Number of subjects enrolled | Romania: 3              |
| Country: Number of subjects enrolled | Russian Federation: 102 |
| Country: Number of subjects enrolled | Slovakia: 9             |
| Country: Number of subjects enrolled | Spain: 15               |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Taiwan: 129        |
| Country: Number of subjects enrolled | Thailand: 89       |
| Country: Number of subjects enrolled | Turkey: 32         |
| Country: Number of subjects enrolled | Ukraine: 222       |
| Country: Number of subjects enrolled | United States: 683 |
| Country: Number of subjects enrolled | Vietnam: 263       |
| Worldwide total number of subjects   | 2761               |
| EEA total number of subjects         | 218                |

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)                      | 1526 |
| From 65 to 84 years                       | 1137 |
| 85 years and over                         | 98   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 385 centers in 25 countries worldwide across the United States (US), Canada, Latin America, Asia and Europe between 26 June 2014 and 04 October 2018. Participants with CKD who were not on dialysis were recruited in this study.

### Pre-assignment

Screening details:

Study had a screening period (up to 6 weeks), treatment period (up to 4 years) and follow-up period (4 weeks after treatment period for those who completed treatment). 2781 participants were randomized, of which 2761 were included in the analysis and 20 were excluded. Only participants included in the analysis are presented in the participant flow.

### Period 1

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

### Arms

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

Arm description:

Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb)  $11\pm 1$  grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Roxadustat         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

The initial dose was 70 mg orally TIW. Dosing continued TIW throughout the treatment period (up to 4 years) unless downward dose adjustment required a change to twice or once weekly.

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

Arm description:

Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Placebo tablets matched to size and strength of roxadustat tablets, orally TIW. Dosing continued TIW

throughout the treatment period (up to 4 years) unless downward dose adjustment required a change to twice or once weekly.

| Number of subjects in period 1           | Roxadustat         | Placebo            |
|------------------------------------------|--------------------|--------------------|
| Started                                  | 1384               | 1377               |
| Received treatment                       | 1384               | 1376               |
| Discontinued treatment                   | 499 <sup>[1]</sup> | 801 <sup>[2]</sup> |
| Completed                                | 1300               | 1247               |
| Not completed                            | 84                 | 130                |
| Incorrect enrolment before randomization | -                  | 1                  |
| Consent withdrawn by subject             | 84                 | 128                |
| Missing                                  | -                  | 1                  |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left. Either resolve this issue or provide a justification.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left. Either resolve this issue or provide a justification.

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Roxadustat |
|-----------------------|------------|

Reporting group description:

Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb)  $11 \pm 1$  grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

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

Reporting group description:

Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

| Reporting group values                                | Roxadustat  | Placebo     | Total |
|-------------------------------------------------------|-------------|-------------|-------|
| Number of subjects                                    | 1384        | 1377        | 2761  |
| Age categorical<br>Units: Subjects                    |             |             |       |
| In utero                                              | 0           | 0           | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0           | 0           | 0     |
| Newborns (0-27 days)                                  | 0           | 0           | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0           | 0           | 0     |
| Children (2-11 years)                                 | 0           | 0           | 0     |
| Adolescents (12-17 years)                             | 0           | 0           | 0     |
| Adults (18-64 years)                                  | 796         | 730         | 1526  |
| From 65-84 years                                      | 547         | 590         | 1137  |
| 85 years and over                                     | 41          | 57          | 98    |
| Age Continuous<br>Units: years                        |             |             |       |
| arithmetic mean                                       | 60.9        | 62.4        |       |
| standard deviation                                    | $\pm 14.67$ | $\pm 14.14$ | -     |
| Sex: Female, Male<br>Units: Subjects                  |             |             |       |
| Female                                                | 820         | 774         | 1594  |
| Male                                                  | 564         | 603         | 1167  |
| Race/Ethnicity, Customized<br>Units: Subjects         |             |             |       |
| White                                                 | 623         | 611         | 1234  |
| Black or African American                             | 112         | 115         | 227   |
| Asian                                                 | 544         | 538         | 1082  |
| Native Hawaiian or other Pacific<br>Islander          | 0           | 2           | 2     |
| American Indian or Alaska Native                      | 24          | 29          | 53    |
| Other                                                 | 81          | 82          | 163   |
| Ethnicity (NIH/OMB)                                   |             |             |       |

|                         |      |      |      |
|-------------------------|------|------|------|
| Units: Subjects         |      |      |      |
| Hispanic or Latino      | 344  | 357  | 701  |
| Not Hispanic or Latino  | 1040 | 1020 | 2060 |
| Unknown or Not Reported | 0    | 0    | 0    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Roxadustat |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
| Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb) 11±1 grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values. |            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Placebo    |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
| Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.                            |            |

### Primary: US Food and Drug Administration (FDA) Analysis: Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | US Food and Drug Administration (FDA) Analysis: Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                  |
| Baseline Hb was defined as the mean of the last 3 central laboratory Hb values from the screening and randomization visits. Mean change in Hb from baseline to mean value from Week 28 to Week 52 was analyzed using a missing at random (MAR) based multiple imputation analysis of covariance (ANCOVA) model with baseline Hb, baseline estimated glomerular filtration rate (eGFR), cardiovascular (CV) history, geographic region and treatment group as fixed effect covariates. The adjusted least squares (LS) mean estimates of change from baseline to mean during Week 28 to Week 52 are presented. The Intention-To-Treat (ITT) analysis set included all participants who were randomized to investigational product (IP) irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. |                                                                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Primary                                                                                                          |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                  |
| Baseline (Day 1, Week 0) and Week 28 to Week 52.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                  |

| End point values                    | Roxadustat      | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 1334            | 1330            |  |  |
| Units: g/dL                         |                 |                 |  |  |
| least squares mean (standard error) | 1.75 (± 0.033)  | 0.40 (± 0.034)  |  |  |

### Statistical analyses

|                                                                                             |                            |
|---------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                  | Treatment Difference in Hb |
| Statistical analysis description:                                                           |                            |
| Difference between groups (roxadustat minus placebo) in LS mean changes; MAR-based multiple |                            |

imputation ANCOVA model.

|                                         |                            |
|-----------------------------------------|----------------------------|
| Comparison groups                       | Roxadustat v Placebo       |
| Number of subjects included in analysis | 2664                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | 1.35                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.27                       |
| upper limit                             | 1.43                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.041                      |

Notes:

[1] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% confidence interval (CI) of the difference between roxadustat and placebo exceeded 0 g/dL.

### Primary: European Union (EU) Health Authorities Analysis: Percentage of Participants With Hb Response During the First 24 Weeks of Treatment

|                 |                                                                                                                                     |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title | European Union (EU) Health Authorities Analysis: Percentage of Participants With Hb Response During the First 24 Weeks of Treatment |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Hb response was defined as: - Hb  $\geq$  11.0 g/dL and Hb increase from baseline by  $\geq$  1.0 g/dL for participants with baseline Hb > 8.0 g/dL; or - Hb increase from baseline by  $\geq$  2.0 g/dL, for participants with baseline Hb  $\leq$  8.0 g/dL at 2 consecutive visits (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (red blood cell [RBC] transfusion, erythropoietin analogue, or intravenous [IV] iron) prior to Hb response. The percentage of participants with an Hb response during the first 24 weeks of treatment is presented. The Full Analysis Set (FAS) included all participants in the ITT analysis set who received at least 1 dose of IP and had baseline Hb and at least 1 post-dose Hb assessment. Participants from the FAS, with data available for analysis are presented.

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

End point timeframe:

Baseline (Day 1, Week 0) up to Week 24.

| End point values                  | Roxadustat      | Placebo         |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 1371            | 1357            |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 77.0            | 8.5             |  |  |

### Statistical analyses

|                            |                                       |
|----------------------------|---------------------------------------|
| Statistical analysis title | Treatment difference in Hb responders |
|----------------------------|---------------------------------------|

**Statistical analysis description:**

Comparison of the percentage of responders for roxadustat versus placebo was analysed using a Cochran-Mantel-Haenszel test adjusting for baseline Hb, baseline eGFR, geographic region and CV history.

|                                         |                         |
|-----------------------------------------|-------------------------|
| Comparison groups                       | Roxadustat v Placebo    |
| Number of subjects included in analysis | 2728                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001                 |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Relative Risk           |
| Point estimate                          | 9.12                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 7.63                    |
| upper limit                             | 10.89                   |

**Secondary: Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52 in Participants With Baseline High Sensitivity C-Reactive Protein (hsCRP) Greater Than the Upper Limit of Normal (ULN)**

|                 |                                                                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52 in Participants With Baseline High Sensitivity C-Reactive Protein (hsCRP) Greater Than the Upper Limit of Normal (ULN) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Baseline hsCRP was quantified from stored biomarker samples obtained at randomization. Baseline Hb was defined as the mean of the last 3 central laboratory Hb values from the screening and randomization visits. Mean change in Hb from baseline to mean value during Week 28 to Week 52 was analyzed using a MAR based multiple imputation ANCOVA model with baseline Hb, baseline eGFR, CV history, geographic region and treatment group as fixed effect covariates. The adjusted LS mean estimates of change from baseline in participants with baseline hsCRP >ULN to mean during Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Only participants who consented to the use of donated biomarker samples and had baseline hsCRP >ULN were included in the analysis.

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

**End point timeframe:**

Baseline (Day 1, Week 0) and Week 28 to Week 52.

| <b>End point values</b>             | Roxadustat      | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 213             | 198             |  |  |
| Units: g/dL                         |                 |                 |  |  |
| least squares mean (standard error) | 1.75 (± 0.087)  | 0.62 (± 0.091)  |  |  |

**Statistical analyses**

|                                                                                                                                                           |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| <b>Statistical analysis title</b>                                                                                                                         | Treatment Difference in Hb |
| Statistical analysis description:<br>Difference between groups (roxadustat minus placebo) in LS mean changes; MAR-based multiple imputation ANCOVA model. |                            |
| Comparison groups                                                                                                                                         | Roxadustat v Placebo       |
| Number of subjects included in analysis                                                                                                                   | 411                        |
| Analysis specification                                                                                                                                    | Pre-specified              |
| Analysis type                                                                                                                                             | superiority <sup>[2]</sup> |
| P-value                                                                                                                                                   | < 0.001                    |
| Method                                                                                                                                                    | ANCOVA                     |
| Parameter estimate                                                                                                                                        | LS Mean Difference         |
| Point estimate                                                                                                                                            | 1.13                       |
| Confidence interval                                                                                                                                       |                            |
| level                                                                                                                                                     | 95 %                       |
| sides                                                                                                                                                     | 2-sided                    |
| lower limit                                                                                                                                               | 0.91                       |
| upper limit                                                                                                                                               | 1.35                       |
| Variability estimate                                                                                                                                      | Standard error of the mean |
| Dispersion value                                                                                                                                          | 0.112                      |

Notes:

[2] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0 g/dL.

## Secondary: Proportion of Total Time of Interpolated Hb Values Greater Than or Equal To 10 g/dL From Week 28 to Week 52

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of Total Time of Interpolated Hb Values Greater Than or Equal To 10 g/dL From Week 28 to Week 52 |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Proportion of total time of interpolated Hb values  $\geq 10$  g/dL was calculated as the time the linearly interpolated curve between measurements  $\geq 10$  g/dL divided by the time between measurements from Week 28 to Week 52. Proportion of total time was analyzed using an ANCOVA model with baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

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

End point timeframe:

Week 28 up to Week 52.

| End point values                    | Roxadustat          | Placebo             |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 1220                | 1145                |  |  |
| Units: proportion of total time     |                     |                     |  |  |
| least squares mean (standard error) | 0.82 ( $\pm$ 0.011) | 0.33 ( $\pm$ 0.011) |  |  |

## Statistical analyses

|                                                                                                                             |                                          |
|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>                                                                                           | Treatment Difference in Total Time of Hb |
| Statistical analysis description:<br>Difference between groups (roxadustat minus placebo) in LS mean changes; ANCOVA model. |                                          |
| Comparison groups                                                                                                           | Roxadustat v Placebo                     |
| Number of subjects included in analysis                                                                                     | 2365                                     |
| Analysis specification                                                                                                      | Pre-specified                            |
| Analysis type                                                                                                               | superiority <sup>[3]</sup>               |
| P-value                                                                                                                     | < 0.001                                  |
| Method                                                                                                                      | ANCOVA                                   |
| Parameter estimate                                                                                                          | LS Mean Difference                       |
| Point estimate                                                                                                              | 0.5                                      |
| Confidence interval                                                                                                         |                                          |
| level                                                                                                                       | 95 %                                     |
| sides                                                                                                                       | 2-sided                                  |
| lower limit                                                                                                                 | 0.47                                     |
| upper limit                                                                                                                 | 0.52                                     |
| Variability estimate                                                                                                        | Standard error of the mean               |
| Dispersion value                                                                                                            | 0.013                                    |

Notes:

[3] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

### **Secondary: Proportion of Total Time of Interpolated Hb Values Within the Interval of 10 to 12 g/dL From Week 28 to Week 52**

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of Total Time of Interpolated Hb Values Within the Interval of 10 to 12 g/dL From Week 28 to Week 52 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

Proportion of total time of interpolated Hb values within the interval of 10 to 12 g/dL was calculated as the time the linearly interpolated curve between measurements were within 10 to 12 g/dL divided by the time between measurements from Week 28 to Week 52. Proportion of total time was analyzed using an ANCOVA model with baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

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

End point timeframe:

Week 28 up to Week 52.

| <b>End point values</b>             | Roxadustat      | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 1220            | 1145            |  |  |
| Units: proportion of total time     |                 |                 |  |  |
| least squares mean (standard error) | 0.70 (± 0.010)  | 0.28 (± 0.010)  |  |  |

## **Statistical analyses**

|                                                                                                                             |                                          |
|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>                                                                                           | Treatment Difference in Total Time of Hb |
| Statistical analysis description:<br>Difference between groups (roxadustat minus placebo) in LS mean changes; ANCOVA model. |                                          |
| Comparison groups                                                                                                           | Roxadustat v Placebo                     |
| Number of subjects included in analysis                                                                                     | 2365                                     |
| Analysis specification                                                                                                      | Pre-specified                            |
| Analysis type                                                                                                               | superiority <sup>[4]</sup>               |
| P-value                                                                                                                     | < 0.001                                  |
| Method                                                                                                                      | ANCOVA                                   |
| Parameter estimate                                                                                                          | LS Mean Difference                       |
| Point estimate                                                                                                              | 0.42                                     |
| Confidence interval                                                                                                         |                                          |
| level                                                                                                                       | 95 %                                     |
| sides                                                                                                                       | 2-sided                                  |
| lower limit                                                                                                                 | 0.4                                      |
| upper limit                                                                                                                 | 0.45                                     |
| Variability estimate                                                                                                        | Standard error of the mean               |
| Dispersion value                                                                                                            | 0.013                                    |

Notes:

[4] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

## Secondary: Mean Change in Low-Density Lipoprotein (LDL) Cholesterol From Baseline to Week 24

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Mean Change in Low-Density Lipoprotein (LDL) Cholesterol From Baseline to Week 24 |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Baseline LDL was defined as the last result obtained prior to randomization. Mean changes in LDL cholesterol from baseline to Week 24 was analyzed using an ANCOVA model with baseline LDL, baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from baseline to Week 24 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

End point timeframe:

Baseline (Day 1, Week 0) and Week 24

|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>             | Roxadustat      | Placebo         |  |  |
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 1147            | 1133            |  |  |
| Units: millimole per liter          |                 |                 |  |  |
| least squares mean (standard error) | -0.38 (± 0.028) | -0.02 (± 0.027) |  |  |

## Statistical analyses

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | Treatment Difference in LDL Cholesterol |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Difference between groups (roxadustat minus placebo) in LS mean changes; ANCOVA model.

|                                         |                            |
|-----------------------------------------|----------------------------|
| Comparison groups                       | Roxadustat v Placebo       |
| Number of subjects included in analysis | 2280                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -0.36                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.42                      |
| upper limit                             | -0.29                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.033                      |

Notes:

[5] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

## Secondary: Time-To-First Instance of Receiving IV Iron, RBC Transfusion or Erythropoietin Analogue as Rescue Therapy

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Time-To-First Instance of Receiving IV Iron, RBC Transfusion or Erythropoietin Analogue as Rescue Therapy |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Time-to-first rescue therapy (IV iron, RBC transfusion or erythropoietin analogue) was calculated as (date of first rescue therapy, or date of censoring if no rescue therapy was taken) minus (date of first dose of IP) +1. Event rate was calculated as (number of participants with event) divided by (the total number of days at risk for event across all participants in given group divided by 365.25) multiplied by 100. The event rate is presented for participants with events. The on-treatment plus 28 days (OT+28) analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored 28 days after last intake of IP.

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

End point timeframe:

Baseline (Day1, Week 0) up to End of Study (EOS) visit (4 weeks after the treatment period) (or up to date of first rescue therapy), with treatment duration up to 4 years.

| End point values                        | Roxadustat      | Placebo         |  |  |
|-----------------------------------------|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 1384            | 1376            |  |  |
| Units: Events per 100 participant years |                 |                 |  |  |
| number (not applicable)                 | 11.90           | 39.76           |  |  |

## Statistical analyses

|                            |                                        |
|----------------------------|----------------------------------------|
| Statistical analysis title | Treatment Difference in Rescue Therapy |
|----------------------------|----------------------------------------|

Statistical analysis description:

Treatments were compared using a Cox proportional hazards model, with baseline Hb and baseline eGFR

as continuous variables used as covariates, and treatment group, CV history and geographic region as fixed effects. The Efron method was used for ties and p-values were calculated using the Wald test.

|                                         |                            |
|-----------------------------------------|----------------------------|
| Comparison groups                       | Roxadustat v Placebo       |
| Number of subjects included in analysis | 2760                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.26                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.23                       |
| upper limit                             | 0.31                       |

Notes:

[6] - Superiority of roxadustat compared with placebo would be declared if the upper limit of the 2-sided 95% CI for the HR was  $\leq 1.0$ .

## Secondary: Time-To-First Instance of Receiving a RBC Transfusion As Rescue Therapy

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Time-To-First Instance of Receiving a RBC Transfusion As Rescue Therapy |
|-----------------|-------------------------------------------------------------------------|

End point description:

Time-to-first RBC rescue therapy was calculated as (date of first RBC rescue therapy, or date of censoring if no rescue therapy was taken) minus (date of first dose of IP) +1. Event rate was calculated as (number of participants with event) divided by (the total number of days at risk for event across all participants in given group divided by 365.25) multiplied by 100. The event rate is presented for participants with events. The OT+28 analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored 28 days after last intake of IP.

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

End point timeframe:

Baseline (Day1, Week 0) up to EOS visit (4 weeks after the treatment period) (or up to date of first RBC rescue therapy), with treatment duration up to 4 years.

| End point values                        | Roxadustat      | Placebo         |  |  |
|-----------------------------------------|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 1384            | 1376            |  |  |
| Units: Events per 100 participant years |                 |                 |  |  |
| number (not applicable)                 | 7.98            | 19.61           |  |  |

## Statistical analyses

|                            |                                         |
|----------------------------|-----------------------------------------|
| Statistical analysis title | Treatment Difference in RBC Transfusion |
|----------------------------|-----------------------------------------|

Statistical analysis description:

Treatments were compared using a Cox proportional hazards model, with baseline Hb and baseline eGFR as continuous variables used as covariates, and treatment group, CV history and geographic region as fixed effects. The Efron method was used for ties and p-values were calculated using the Wald test.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 2760                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[7]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.37                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.3                        |
| upper limit                             | 0.44                       |

Notes:

[7] - Superiority of roxadustat compared with placebo would be declared if the upper limit of the 2-sided 95% CI for the HR was  $\leq 1.0$ .

### Secondary: Mean Change From Baseline in Short Form 36 (SF-36) Vitality Sub-Score From Week 12 to Week 28

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Mean Change From Baseline in Short Form 36 (SF-36) Vitality Sub-Score From Week 12 to Week 28 |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

SF-36 is a Quality of Life (QoL) scale comprising 8 domains of health status: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Each domain score is on a scale from 0-100 (worst health possible to best health possible); higher scores indicate better health status. Mean change in SF-36 Vitality sub-score from baseline to mean from Week 12 to Week 28 was analyzed using a mixed model for repeated measures (MMRM) with terms for baseline score, treatment group, baseline Hb, baseline eGFR, CV history, geographic region, visit and treatment-by-visit interaction as fixed effects and participant as random effect. The adjusted LS mean estimates of change from baseline to mean score from Week 12 to Week 28 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

End point timeframe:

Baseline (Day 1, Week 0) and Week 12 to Week 28.

| End point values                    | Roxadustat          | Placebo             |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 1279                | 1235                |  |  |
| Units: scores on a scale            |                     |                     |  |  |
| least squares mean (standard error) | 1.59 ( $\pm$ 0.231) | 1.15 ( $\pm$ 0.233) |  |  |

### Statistical analyses

|                            |                                        |
|----------------------------|----------------------------------------|
| Statistical analysis title | Treatment Difference in SF-36 Vitality |
|----------------------------|----------------------------------------|

Statistical analysis description:

Difference between groups (roxadustat minus placebo) in LS mean changes; MMRM analysis.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 2514                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[8]</sup> |
| P-value                                 | = 0.12                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | 0.44                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.11                      |
| upper limit                             | 0.99                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.283                      |

Notes:

[8] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

## Secondary: Annual Rate of eGFR Change From Baseline Prior to the Initiation of Dialysis or Kidney Transplant

|                 |                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------|
| End point title | Annual Rate of eGFR Change From Baseline Prior to the Initiation of Dialysis or Kidney Transplant |
|-----------------|---------------------------------------------------------------------------------------------------|

End point description:

Baseline eGFR was defined as the mean of all available central laboratory values prior to or at randomization. Rate of change in eGFR from baseline during the entire treatment period (in milliliters/minute/1.73 meters squared/years [mL/min/1.73m<sup>2</sup>/years]) was estimated using a random effects model using all post baseline eGFR values prior to initiation of dialysis/transplant. Baseline eGFR, baseline Hb, geographic region, CV history, treatment group and post baseline eGFR measurement time were used as fixed effects and participant and time (years) as random effects, ie, random intercept and slope. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

End point timeframe:

Baseline (Day1, Week 0) up to EOS visit (4 weeks after the treatment period), with treatment duration up to 4 years.

| End point values                                    | Roxadustat      | Placebo         |  |  |
|-----------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed                         | 1326            | 1314            |  |  |
| Units: eGFR rate (mL/min/1.73m <sup>2</sup> /years) |                 |                 |  |  |
| number (not applicable)                             | -3.70           | -3.19           |  |  |

## Statistical analyses

|                            |                                   |
|----------------------------|-----------------------------------|
| Statistical analysis title | Treatment Difference in eGFR Rate |
|----------------------------|-----------------------------------|

Statistical analysis description:

Difference between groups (roxadustat minus placebo) in rate of change in eGFR; random effects analysis.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 2640                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | = 0.046 <sup>[9]</sup>     |
| Method                                  | Random Effects Analysis    |
| Parameter estimate                      | Rate of Change Difference  |
| Point estimate                          | -0.51                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1                         |
| upper limit                             | -0.01                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.254                      |

Notes:

[9] - Nominal p-value (as prior sequential outcome measure p-value did not meet < 0.05).

### Secondary: Mean Change From Baseline in SF-36 Physical Functioning Sub-Score From Week 12 to Week 28

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Mean Change From Baseline in SF-36 Physical Functioning Sub-Score From Week 12 to Week 28 |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

SF-36 is a QoL scale comprising 8 domains of health status: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Each domain score is on a scale from 0-100 (worst health possible to best health possible); higher scores indicate better health status. Mean change in SF-36 Physical Functioning sub-score from baseline to mean from Week 12 to Week 28 was analyzed using a MMRM with terms for baseline score, treatment group, baseline Hb, baseline eGFR, CV history, geographic region, visit and treatment-by-visit interaction as fixed effects and participant as random effect. The adjusted LS mean estimates of change from baseline to mean score from Week 12 to Week 28 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

End point timeframe:

Baseline (Day 1, Week 0) and Week 12 to Week 28.

| End point values                    | Roxadustat      | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 1279            | 1234            |  |  |
| Units: scores on a scale            |                 |                 |  |  |
| least squares mean (standard error) | 0.14 (± 0.222)  | -0.39 (± 0.224) |  |  |

### Statistical analyses

|                            |                                                    |
|----------------------------|----------------------------------------------------|
| Statistical analysis title | Treatment Difference in SF-36 Physical Functioning |
|----------------------------|----------------------------------------------------|

Statistical analysis description:

Difference between groups (roxadustat minus placebo) in LS mean changes; MMRM analysis.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | Roxadustat v Placebo |
|-------------------|----------------------|

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 2513                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[10]</sup> |
| P-value                                 | = 0.051 <sup>[11]</sup>     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LS Mean Difference          |
| Point estimate                          | 0.52                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0                           |
| upper limit                             | 1.05                        |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.269                       |

Notes:

[10] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

[11] - Nominal p-value (as prior sequential outcome measure p-value did not meet < 0.05).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of randomization up to EOS visit (4 weeks after the treatment period), with treatment duration up to 4 years.

Adverse event reporting additional description:

The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched to 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

|                       |            |
|-----------------------|------------|
| Reporting group title | Roxadustat |
|-----------------------|------------|

Reporting group description:

Participants received roxadustat tablets orally TIW. The initial dose was 70 mg TIW and was titrated to achieve and maintain Hb 11±1 g/dL. Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

| Serious adverse events                                              | Placebo                | Roxadustat             |  |
|---------------------------------------------------------------------|------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                        |                        |  |
| subjects affected / exposed                                         | 749 / 1377<br>(54.39%) | 795 / 1384<br>(57.44%) |  |
| number of deaths (all causes)                                       | 245                    | 284                    |  |
| number of deaths resulting from adverse events                      | 213                    | 262                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |  |
| Acute myeloid leukaemia                                             |                        |                        |  |
| subjects affected / exposed                                         | 0 / 1377 (0.00%)       | 1 / 1384 (0.07%)       |  |
| occurrences causally related to treatment / all                     | 0 / 0                  | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Adenocarcinoma of colon                                             |                        |                        |  |
| subjects affected / exposed                                         | 1 / 1377 (0.07%)       | 0 / 1384 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Bladder cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cancer female                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cancer metastatic                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervix carcinoma                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon adenoma                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colorectal cancer metastatic                    |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial cancer                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiglottic carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric neoplasm                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal tract adenoma                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatocellular carcinoma                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal cancer                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive ductal breast carcinoma                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leiomyoma                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lip squamous cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung neoplasm                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung carcinoma cell type unspecified stage IV   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lung neoplasm malignant                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Malignant melanoma                              |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic neoplasm                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Myelodysplastic syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelofibrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neoplasm of appendix                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine tumour of the lung               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal carcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papillary thyroid cancer                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plasma cell myeloma                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Prostate cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small cell lung cancer                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Squamous cell carcinoma of skin                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the vagina           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine leiomyoma                               |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Accelerated hypertension                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic aneurysm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic aneurysm rupture                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aortic stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Arteriosclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Arteriovenous fistula                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Circulatory collapse                            |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Deep vein thrombosis                            |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 15 / 1384 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 15            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Distributive shock                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Dry gangrene                                    |                  |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Embolism venous                                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Extremity necrosis                              |                  |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Haematoma                                       |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Haemorrhage                                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypertension                                    |                  |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 16 / 1377 (1.16%) | 17 / 1384 (1.23%) |  |
| occurrences causally related to treatment / all | 1 / 16            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive crisis                             |                   |                   |  |
| subjects affected / exposed                     | 27 / 1377 (1.96%) | 33 / 1384 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 31            | 0 / 51            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive emergency                          |                   |                   |  |
| subjects affected / exposed                     | 21 / 1377 (1.53%) | 21 / 1384 (1.52%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 24            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypotension                                     |                   |                   |  |
| subjects affected / exposed                     | 8 / 1377 (0.58%)  | 6 / 1384 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 1 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypovolaemic shock                              |                   |                   |  |
| subjects affected / exposed                     | 6 / 1377 (0.44%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             |  |
| Iliac artery perforation                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Jugular vein thrombosis                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Lymphocele                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant hypertension                          |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paget-Schroetter syndrome                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pallor                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Peripheral artery occlusion                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral venous disease                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post thrombotic syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shock haemorrhagic                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            |  |
| Steal syndrome                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis superficial                    |                  |                  |  |

|                                                      |                  |                   |  |
|------------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                          | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| Varicose ulceration                                  |                  |                   |  |
| subjects affected / exposed                          | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| Vascular occlusion                                   |                  |                   |  |
| subjects affected / exposed                          | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| Venous thrombosis                                    |                  |                   |  |
| subjects affected / exposed                          | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| Venous thrombosis limb                               |                  |                   |  |
| subjects affected / exposed                          | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| Visceral congestion                                  |                  |                   |  |
| subjects affected / exposed                          | 1 / 1377 (0.07%) | 0 / 1384 (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       |                  |                   |  |
| Abortion spontaneous                                 |                  |                   |  |
| subjects affected / exposed                          | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |
| General disorders and administration site conditions |                  |                   |  |
| Asthenia                                             |                  |                   |  |
| subjects affected / exposed                          | 9 / 1377 (0.65%) | 13 / 1384 (0.94%) |  |
| occurrences causally related to treatment / all      | 0 / 9            | 0 / 14            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Catheter site haemorrhage                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Catheter site pain                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chest pain                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Death                                           |                   |                   |  |
| subjects affected / exposed                     | 28 / 1377 (2.03%) | 43 / 1384 (3.11%) |  |
| occurrences causally related to treatment / all | 1 / 28            | 0 / 43            |  |
| deaths causally related to treatment / all      | 1 / 28            | 0 / 43            |  |
| Device related thrombosis                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fatigue                                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Generalised oedema                              |                   |                   |  |
| subjects affected / exposed                     | 7 / 1377 (0.51%)  | 17 / 1384 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 25            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hernia pain                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Implant site extravasation                      |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Implant site necrosis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inflammation                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple organ dysfunction syndrome             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema                                          |                  |                  |  |
| subjects affected / exposed                     | 7 / 1377 (0.51%) | 7 / 1384 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema due to renal disease                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 7 / 1384 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pacemaker generated arrhythmia                  |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Peripheral swelling                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pyrexia                                         |                   |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%)  | 6 / 1384 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Stenosis                                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sudden cardiac death                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Sudden death                                    |                   |                  |  |
| subjects affected / exposed                     | 11 / 1377 (0.80%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 5            |  |
| Immune system disorders                         |                   |                  |  |
| Anaphylactic shock                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Device allergy                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hypersensitivity                                |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kidney transplant rejection                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal transplant failure                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transplant rejection                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysfunctional uterine bleeding                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Menorrhagia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cyst ruptured                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cyst torsion                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian mass                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic prolapse                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatic fibrosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatic mass                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatomegaly                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute pulmonary oedema                          |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 22 / 1377 (1.60%) | 13 / 1384 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 25            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Acute respiratory distress syndrome             |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Acute respiratory failure                       |                   |                   |  |
| subjects affected / exposed                     | 20 / 1377 (1.45%) | 12 / 1384 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 5             |  |
| Aspiration                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Asthma                                          |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchial fistula                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis chronic                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic obstructive pulmonary disease           |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 8 / 1377 (0.58%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Dyspnoea                                        |                   |                   |  |
| subjects affected / exposed                     | 12 / 1377 (0.87%) | 11 / 1384 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| Dyspnoea exertional                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Epistaxis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haemoptysis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haemothorax                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Laryngeal stenosis                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Obstructive airways disorder                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oropharyngeal pain                              |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pleural effusion                                |                   |                   |  |
| subjects affected / exposed                     | 16 / 1377 (1.16%) | 15 / 1384 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pleural thickening                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pleurisy                                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia aspiration                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Pneumonitis                                     |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumothorax                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary alveolar haemorrhage                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary congestion                            |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pulmonary embolism                              |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 5 / 1384 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Pulmonary fibrosis                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pulmonary haemorrhage                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pulmonary hypertension                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary oedema                                |                   |                   |  |
| subjects affected / exposed                     | 16 / 1377 (1.16%) | 17 / 1384 (1.23%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Respiratory alkalosis                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory distress                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory failure                             |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 9 / 1377 (0.65%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 6            | 0 / 2            |  |
| Tracheal stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract inflammation            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Alcohol withdrawal syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anxiety                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar disorder                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Completed suicide                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium                                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Insomnia                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental status changes                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paranoia                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular cognitive impairment                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Device dislocation                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device failure                                  |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Bile duct stenosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis acute                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis chronic                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholelithiasis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholestasis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic hepatic failure                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cirrhosis alcoholic                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhagic hepatic cyst                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Hepatitis acute                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis alcoholic                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperbilirubinaemia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaundice                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Anticoagulation drug level increased            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood bicarbonate decreased                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood bilirubin increased                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood creatine increased                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood creatinine increased                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood glucose abnormal                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood glucose increased                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure decreased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure increased                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Blood urine present                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coagulation factor decreased                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic enzyme increased                        |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Troponin increased                              |                  |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Injury, poisoning and procedural complications  |                  |                   |  |
| Anastomotic stenosis                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ankle fracture                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriovenous fistula occlusion                 |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 7 / 1384 (0.51%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriovenous fistula site complication         |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriovenous fistula site haemorrhage          |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriovenous fistula thrombosis                |                  |                   |  |
| subjects affected / exposed                     | 9 / 1377 (0.65%) | 18 / 1384 (1.30%) |  |
| occurrences causally related to treatment / all | 1 / 9            | 1 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chemical peritonitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chemical poisoning                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chest injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Comminuted fracture                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Complications of transplanted kidney            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Compression fracture                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dialysis disequilibrium syndrome                |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dialysis related complication                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial bones fracture                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral neck fracture                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femur fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Forearm fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fractured sacrum                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heat stroke                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (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                     | 6 / 1377 (0.44%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury                                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lip injury                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle injury                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periorbital haemorrhage                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal dialysis complication                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural complication                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural hypotension                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural pain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seroma                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shunt malfunction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shunt occlusion                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal compression fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord injury cervical                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Spinal fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spleen contusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stoma obstruction                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stoma site haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subarachnoid haemorrhage                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transplant dysfunction                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic liver injury                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular access malfunction                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular access site thrombosis                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 6 / 1384 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft complication                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular pseudoaneurysm                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound dehiscence                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound haematoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Congenital cystic kidney disease                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrocele                                       |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac disorders                               |                   |                   |  |
| Acute coronary syndrome                         |                   |                   |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%)  | 8 / 1384 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Acute left ventricular failure                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%)  | 5 / 1384 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Acute myocardial infarction                     |                   |                   |  |
| subjects affected / exposed                     | 27 / 1377 (1.96%) | 26 / 1384 (1.88%) |  |
| occurrences causally related to treatment / all | 1 / 31            | 0 / 28            |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 6             |  |
| Angina pectoris                                 |                   |                   |  |
| subjects affected / exposed                     | 9 / 1377 (0.65%)  | 10 / 1384 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina unstable                                 |                   |                   |  |
| subjects affected / exposed                     | 10 / 1377 (0.73%) | 10 / 1384 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arrhythmia                                      |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 6 / 1384 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Aortic valve stenosis                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arteriosclerosis coronary artery                |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| 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                     | 12 / 1377 (0.87%) | 10 / 1384 (0.72%) |  |
| occurrences causally related to treatment / all | 1 / 15            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial flutter                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradyarrhythmia                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bundle branch block left                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradycardia                                     |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 4 / 1377 (0.29%)  | 9 / 1384 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 9             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 6             |  |
| Cardiac asthma                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac failure                                 |                   |                   |  |
| subjects affected / exposed                     | 32 / 1377 (2.32%) | 25 / 1384 (1.81%) |  |
| occurrences causally related to treatment / all | 0 / 35            | 0 / 31            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 6             |  |
| Cardiac failure acute                           |                   |                   |  |
| subjects affected / exposed                     | 14 / 1377 (1.02%) | 8 / 1384 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 3             |  |
| Cardiac failure chronic                         |                   |                   |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%)  | 4 / 1384 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac failure congestive                      |                   |                   |  |
| subjects affected / exposed                     | 31 / 1377 (2.25%) | 33 / 1384 (2.38%) |  |
| occurrences causally related to treatment / all | 1 / 42            | 0 / 41            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 7             |  |
| Cardiac tamponade                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardio-respiratory arrest                       |                   |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%)  | 6 / 1384 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 5             |  |
| Cardiogenic shock                               |                   |                   |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3             |  |
| Cardiomegaly                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiomyopathy                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiopulmonary failure                         |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3             |  |
| Chronic left ventricular failure                |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Congestive cardiomyopathy                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Coronary artery disease                         |                  |                   |  |
| subjects affected / exposed                     | 7 / 1377 (0.51%) | 12 / 1384 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Coronary artery insufficiency                   |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Coronary artery stenosis                        |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart valve incompetence                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart valve stenosis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive cardiomyopathy                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ischaemic cardiomyopathy                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular dysfunction                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Left ventricular failure                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Left ventricular hypertrophy                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic cardiomyopathy                        |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mitral valve disease                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Mitral valve incompetence                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myocardial infarction                           |                   |                   |  |
| subjects affected / exposed                     | 13 / 1377 (0.94%) | 14 / 1384 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 6             |  |
| Myocardial ischaemia                            |                   |                   |  |
| subjects affected / exposed                     | 8 / 1377 (0.58%)  | 4 / 1384 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 0             |  |
| Pericardial effusion                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulseless electrical activity                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Right ventricular failure                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sinoatrial block                                |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus arrest                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus bradycardia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus node dysfunction                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular arrhythmia                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular extrasystoles                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Aphasia                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Autonomic nervous system imbalance              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar infarction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar stroke                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral haematoma                              |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cerebral haemorrhage                            |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 9 / 1384 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 1 / 9             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 4             |  |
| Cerebral infarction                             |                   |                   |  |
| subjects affected / exposed                     | 8 / 1377 (0.58%)  | 13 / 1384 (0.94%) |  |
| occurrences causally related to treatment / all | 1 / 9             | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cerebrovascular accident                        |                   |                   |  |
| subjects affected / exposed                     | 11 / 1377 (0.80%) | 15 / 1384 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             |  |
| Cerebrovascular disorder                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cerebrovascular insufficiency                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cervical cord compression                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Coma                                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Coma uraemic                                    |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Dementia                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia Alzheimer's type                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Demyelination                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depressed level of consciousness                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic hyperglycaemic coma                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic hyperosmolar coma                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidotic hyperglycaemic coma       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Diabetic neuropathy                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial paralysis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Facial spasm                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Generalised tonic-clonic seizure                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic stroke                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 1377 (0.44%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 2            |  |
| Haemorrhage intracranial                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Headache                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive encephalopathy                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intercostal neuralgia                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic cerebral infarction                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ischaemic stroke                                |                  |                  |  |
| subjects affected / exposed                     | 7 / 1377 (0.51%) | 9 / 1384 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Lacunar infarction                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lacunar stroke                                  |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic encephalopathy                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Myoclonus                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurodegenerative disorder                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Neuroleptic malignant syndrome                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Neuropathy peripheral                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Occipital neuralgia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraparesis                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial seizures                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyneuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post stroke seizure                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sciatica                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (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                     | 2 / 1377 (0.15%) | 6 / 1384 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Senile dementia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Somnolence                                      |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope                                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thalamic infarction                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Thalamus haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uraemic encephalopathy                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| VIth nerve paralysis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular encephalopathy                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertebrobasilar insufficiency                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo CNS origin                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular migraine                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coagulopathy                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Evans syndrome                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemolytic uraemic syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic anaemia                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Histiocytosis haematophagic                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypocoagulable state                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron deficiency anaemia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukocytosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Vertigo                                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo positional                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular ataxia                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular disorder                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Blindness unilateral                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cataract                                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic retinopathy                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ulcerative keratitis                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual acuity reduced                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual impairment                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vitreous haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal adhesions                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Abdominal discomfort                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain lower                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal wall haematoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fistula                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal incontinence                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Crohn's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic gastroparesis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic gastropathy                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 9 / 1384 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dieulafoy's vascular malformation               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal haemorrhagic            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenitis haemorrhagic                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysphagia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis haemorrhagic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erosive duodenitis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral hernia incarcerated                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Functional gastrointestinal disorder            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric polyps                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastritis                                       |                   |                   |  |
| subjects affected / exposed                     | 15 / 1377 (1.09%) | 18 / 1384 (1.30%) |  |
| occurrences causally related to treatment / all | 1 / 18            | 0 / 24            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastritis erosive                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Gastritis haemorrhagic                          |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroduodenitis haemorrhagic                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal disorder                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal haemorrhage                    |                   |                   |  |
| subjects affected / exposed                     | 15 / 1377 (1.09%) | 20 / 1384 (1.45%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 1 / 20            |  |
| deaths causally related to treatment / all      | 0 / 0             | 1 / 3             |  |
| Gastrointestinal inflammation                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrooesophageal reflux disease                |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematemesis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic ascites                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic erosive gastritis                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoidal haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileal perforation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus                                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired gastric emptying                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated umbilical hernia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia strangulated                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal obstruction                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine perforation                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mallory-Weiss syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Melaena                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mesenteric artery thrombosis                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea                                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal ulcer                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal varices haemorrhage                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis ulcerative                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic cyst                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer perforation                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal adhesions                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal cloudy effluent                      |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Peritoneal haemorrhage                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumatosis intestinalis                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Rectal haemorrhage                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Small intestinal haemorrhage                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Small intestinal obstruction                    |                  |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Umbilical hernia                                |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Upper gastrointestinal haemorrhage              |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 11 / 1384 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2             |  |
| Uraemic gastropathy                             |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Blister                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Decubitus ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis atopic                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot                                   |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 6 / 1384 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Diabetic ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papule                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrobiosis lipoidica diabetorum                |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rash                                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Skin ulcer                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Toxic epidermal necrolysis                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stevens-Johnson syndrome                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| 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                     | 32 / 1377 (2.32%) | 41 / 1384 (2.96%) |  |
| occurrences causally related to treatment / all | 0 / 33            | 0 / 48            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Anuria                                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Azotaemia                                       |                   |                   |  |
| subjects affected / exposed                     | 60 / 1377 (4.36%) | 61 / 1384 (4.41%) |  |
| occurrences causally related to treatment / all | 0 / 79            | 0 / 73            |  |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 14            |  |
| Chronic kidney disease                          |                   |                   |  |

|                                                 |                     |                     |  |
|-------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed                     | 7 / 1377 (0.51%)    | 8 / 1384 (0.58%)    |  |
| occurrences causally related to treatment / all | 0 / 7               | 0 / 8               |  |
| deaths causally related to treatment / all      | 0 / 5               | 0 / 7               |  |
| Cystitis haemorrhagic                           |                     |                     |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)    | 1 / 1384 (0.07%)    |  |
| occurrences causally related to treatment / all | 0 / 0               | 0 / 2               |  |
| deaths causally related to treatment / all      | 0 / 0               | 0 / 0               |  |
| Diabetic nephropathy                            |                     |                     |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)    | 1 / 1384 (0.07%)    |  |
| occurrences causally related to treatment / all | 0 / 1               | 0 / 1               |  |
| deaths causally related to treatment / all      | 0 / 1               | 0 / 0               |  |
| End stage renal disease                         |                     |                     |  |
| subjects affected / exposed                     | 201 / 1377 (14.60%) | 199 / 1384 (14.38%) |  |
| occurrences causally related to treatment / all | 0 / 211             | 1 / 211             |  |
| deaths causally related to treatment / all      | 0 / 11              | 0 / 11              |  |
| Glomerulonephritis                              |                     |                     |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)    | 1 / 1384 (0.07%)    |  |
| occurrences causally related to treatment / all | 0 / 1               | 0 / 2               |  |
| deaths causally related to treatment / all      | 0 / 0               | 0 / 0               |  |
| Glomerulonephritis chronic                      |                     |                     |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)    | 2 / 1384 (0.14%)    |  |
| occurrences causally related to treatment / all | 0 / 1               | 0 / 2               |  |
| deaths causally related to treatment / all      | 0 / 0               | 0 / 2               |  |
| Haematuria                                      |                     |                     |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)    | 1 / 1384 (0.07%)    |  |
| occurrences causally related to treatment / all | 0 / 0               | 0 / 1               |  |
| deaths causally related to treatment / all      | 0 / 0               | 0 / 0               |  |
| Nephritic syndrome                              |                     |                     |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)    | 0 / 1384 (0.00%)    |  |
| occurrences causally related to treatment / all | 0 / 1               | 0 / 0               |  |
| deaths causally related to treatment / all      | 0 / 0               | 0 / 0               |  |
| Nephrolithiasis                                 |                     |                     |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephropathy toxic                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive uropathy                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedematous kidney                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oliguria                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyuria                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelocaliectasis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal atrophy                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal colic                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cyst                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cyst haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal impairment                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal pain                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal papillary necrosis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal pelvis fistula                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal tubular necrosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tubulointerstitial nephritis                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ureteric obstruction                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureteric stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureterolithiasis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary fistula                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract inflammation                      |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract obstruction                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Adrenal insufficiency                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Goitre                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperparathyroidism                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperparathyroidism secondary                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical spinal stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Flank pain                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gouty arthritis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemarthrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar spinal stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal chest pain                      |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myalgia                                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myositis                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteoarthritis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pain in extremity                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhabdomyolysis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal osteoarthritis                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic lupus erythematosus                    |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Infections and infestations</b>              |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute hepatitis B                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriovenous fistula site infection            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriovenous graft site infection              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacteraemia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial infection                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone tuberculosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchitis                                      |                  |                  |  |
| subjects affected / exposed                     | 9 / 1377 (0.65%) | 7 / 1384 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbuncle                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac valve abscess                           |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Catheter site cellulitis                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Catheter site infection                         |                   |                   |  |
| subjects affected / exposed                     | 8 / 1377 (0.58%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis                                      |                   |                   |  |
| subjects affected / exposed                     | 13 / 1377 (0.94%) | 24 / 1384 (1.73%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 27            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis gangrenous                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clostridial infection                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clostridium difficile colitis                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 4 / 1384 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Clostridium difficile infection                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cystitis                                        |                   |                   |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cystitis bacterial                              |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cytomegalovirus infection                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cytomegalovirus nephritis                       |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Dengue fever                                    |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Device related infection                        |                  |                   |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 14 / 1384 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Device related sepsis                           |                  |                   |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Diabetic foot infection                         |                  |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Diabetic gangrene                               |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea infectious                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Emphysematous cystitis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Emphysematous pyelonephritis                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Empyema                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis bacterial                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endotoxic shock                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Enteritis infectious                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterobacter sepsis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterococcal sepsis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiglottitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia urinary tract infection             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fungaemia                                       |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fungal oesophagitis                             |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fungal peritonitis                              |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Furuncle                                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gangrene                                        |                  |                   |  |
| subjects affected / exposed                     | 7 / 1377 (0.51%) | 10 / 1384 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastroenteritis                                 |                  |                   |  |
| subjects affected / exposed                     | 8 / 1377 (0.58%) | 13 / 1384 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastroenteritis bacterial                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastroenteritis viral                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Gastrointestinal infection                      |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| H1N1 influenza                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Helicobacter gastritis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis B                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis B reactivation                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis C                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes virus infection                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected lymphocoele                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infective aneurysm                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal tuberculosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kidney infection                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Klebsiella sepsis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Localised infection                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 1377 (0.36%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lung abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| 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                     | 3 / 1377 (0.22%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymph node tuberculosis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasopharyngitis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal candidiasis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orchitis                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Osteomyelitis                                   |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis acute                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis chronic                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Otitis media chronic                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Parvovirus infection                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Perineal abscess                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Perinephric abscess                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Peritonitis                                     |                   |                   |  |
| subjects affected / exposed                     | 14 / 1377 (1.02%) | 15 / 1384 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Peritonitis bacterial                           |                   |                   |  |

|                                                 |                   |                    |  |
|-------------------------------------------------|-------------------|--------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Peritonsillar abscess                           |                   |                    |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pharyngitis                                     |                   |                    |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pleural infection                               |                   |                    |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pneumonia                                       |                   |                    |  |
| subjects affected / exposed                     | 88 / 1377 (6.39%) | 113 / 1384 (8.16%) |  |
| occurrences causally related to treatment / all | 1 / 107           | 0 / 149            |  |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 12             |  |
| Pneumonia bacterial                             |                   |                    |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 2 / 1384 (0.14%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2              |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1              |  |
| Pneumonia influenzal                            |                   |                    |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pneumonia klebsiella                            |                   |                    |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0              |  |
| Pneumonia mycoplasmal                           |                   |                    |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia viral                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural cellulitis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural pneumonia                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomembranous colitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomonas infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary tuberculosis                          |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Purulence                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyelonephritis                                  |                   |                   |  |
| subjects affected / exposed                     | 5 / 1377 (0.36%)  | 8 / 1384 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 9             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyelonephritis acute                            |                   |                   |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%)  | 6 / 1384 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyelonephritis chronic                          |                   |                   |  |
| subjects affected / exposed                     | 11 / 1377 (0.80%) | 11 / 1384 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pyoderma                                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyonephrosis                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal cyst infection                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory tract infection                     |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sepsis                                          |                   |                   |  |
| subjects affected / exposed                     | 23 / 1377 (1.67%) | 49 / 1384 (3.54%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 51            |  |
| deaths causally related to treatment / all      | 0 / 8             | 0 / 26            |  |
| Septic shock                                    |                   |                   |  |
| subjects affected / exposed                     | 15 / 1377 (1.09%) | 18 / 1384 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 14            |  |
| Sinusitis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Staphylococcal bacteraemia                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Staphylococcal infection                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Staphylococcal sepsis                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stenotrophomonas sepsis                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Streptococcal bacteraemia                       |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal endocarditis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous abscess                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Taeniasis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheobronchitis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tuberculosis                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 5 / 1384 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Typhoid fever                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection                         |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 26 / 1377 (1.89%) | 36 / 1384 (2.60%) |  |
| occurrences causally related to treatment / all | 0 / 32            | 0 / 38            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Urinary tract infection bacterial               |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urosepsis                                       |                   |                   |  |
| subjects affected / exposed                     | 6 / 1377 (0.44%)  | 8 / 1384 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Vascular access site infection                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vestibular neuronitis                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral infection                                 |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Acidosis                                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Adult failure to thrive                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Calciophylaxis                                  |                   |                   |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Decreased appetite                              |                   |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Dehydration                                     |                   |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%)  | 8 / 1384 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Diabetes mellitus                               |                   |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Diabetes mellitus inadequate control            |                   |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Diabetic ketoacidosis                           |                   |                  |  |
| subjects affected / exposed                     | 10 / 1377 (0.73%) | 6 / 1384 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1            |  |
| Diabetic metabolic decompensation               |                   |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Electrolyte imbalance                           |                   |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Failure to thrive                               |                   |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fluid overload                                  |                   |                   |  |
| subjects affected / exposed                     | 22 / 1377 (1.60%) | 20 / 1384 (1.45%) |  |
| occurrences causally related to treatment / all | 0 / 27            | 0 / 28            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Fluid retention                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Food aversion                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gout                                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 4 / 1384 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypercalcaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperglycaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 9 / 1377 (0.65%)  | 16 / 1384 (1.16%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Hyperglycaemic hyperosmolar nonketotic syndrome |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperinsulinaemic hypoglycaemia                 |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 0 / 1384 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperkalaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 25 / 1377 (1.82%) | 41 / 1384 (2.96%) |  |
| occurrences causally related to treatment / all | 0 / 35            | 2 / 53            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Hypernatraemia                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 1 / 1384 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hyperuricaemia                                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Hypervolaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1377 (0.00%)  | 4 / 1384 (0.29%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypocalcaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%)  | 2 / 1384 (0.14%)  |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypoglycaemia                                   |                   |                   |  |
| subjects affected / exposed                     | 26 / 1377 (1.89%) | 32 / 1384 (2.31%) |  |
| occurrences causally related to treatment / all | 0 / 27            | 0 / 38            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypokalaemia                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%)  | 3 / 1384 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Hyponatraemia                                   |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 1377 (0.44%) | 7 / 1384 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 3 / 1384 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron deficiency                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ketoacidosis                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ketosis                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 0 / 1384 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malnutrition                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 1377 (0.29%) | 4 / 1384 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Metabolic acidosis                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 1377 (0.22%) | 7 / 1384 (0.51%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |  |
| Type 1 diabetes mellitus                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1377 (0.15%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Type 2 diabetes mellitus                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1377 (0.07%) | 1 / 1384 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Placebo             | Roxadustat          |  |
|-------------------------------------------------------|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                     |                     |  |
| subjects affected / exposed                           | 757 / 1377 (54.97%) | 839 / 1384 (60.62%) |  |
| Vascular disorders                                    |                     |                     |  |
| Hypertension                                          |                     |                     |  |
| subjects affected / exposed                           | 117 / 1377 (8.50%)  | 148 / 1384 (10.69%) |  |
| occurrences (all)                                     | 151                 | 190                 |  |
| Nervous system disorders                              |                     |                     |  |
| Dizziness                                             |                     |                     |  |
| subjects affected / exposed                           | 86 / 1377 (6.25%)   | 74 / 1384 (5.35%)   |  |
| occurrences (all)                                     | 113                 | 91                  |  |
| Headache                                              |                     |                     |  |
| subjects affected / exposed                           | 82 / 1377 (5.95%)   | 93 / 1384 (6.72%)   |  |
| occurrences (all)                                     | 96                  | 122                 |  |
| General disorders and administration site conditions  |                     |                     |  |
| Oedema peripheral                                     |                     |                     |  |
| subjects affected / exposed                           | 106 / 1377 (7.70%)  | 144 / 1384 (10.40%) |  |
| occurrences (all)                                     | 135                 | 192                 |  |
| Gastrointestinal disorders                            |                     |                     |  |
| Constipation                                          |                     |                     |  |
| subjects affected / exposed                           | 88 / 1377 (6.39%)   | 91 / 1384 (6.58%)   |  |
| occurrences (all)                                     | 101                 | 126                 |  |
| Diarrhoea                                             |                     |                     |  |
| subjects affected / exposed                           | 117 / 1377 (8.50%)  | 138 / 1384 (9.97%)  |  |
| occurrences (all)                                     | 156                 | 190                 |  |
| Nausea                                                |                     |                     |  |
| subjects affected / exposed                           | 103 / 1377 (7.48%)  | 124 / 1384 (8.96%)  |  |
| occurrences (all)                                     | 127                 | 171                 |  |
| Vomiting                                              |                     |                     |  |

|                                                                                                                   |                          |                            |  |
|-------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                  | 67 / 1377 (4.87%)<br>85  | 75 / 1384 (5.42%)<br>90    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)      | 69 / 1377 (5.01%)<br>91  | 105 / 1384 (7.59%)<br>123  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                      | 64 / 1377 (4.65%)<br>80  | 70 / 1384 (5.06%)<br>85    |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 80 / 1377 (5.81%)<br>89  | 68 / 1384 (4.91%)<br>84    |  |
| Renal and urinary disorders<br>End stage renal disease<br>subjects affected / exposed<br>occurrences (all)        | 85 / 1377 (6.17%)<br>86  | 93 / 1384 (6.72%)<br>93    |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 53 / 1377 (3.85%)<br>61  | 73 / 1384 (5.27%)<br>85    |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 57 / 1377 (4.14%)<br>69  | 70 / 1384 (5.06%)<br>87    |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 64 / 1377 (4.65%)<br>76  | 72 / 1384 (5.20%)<br>80    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                             | 75 / 1377 (5.45%)<br>100 | 95 / 1384 (6.86%)<br>137   |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                       | 94 / 1377 (6.83%)<br>135 | 152 / 1384 (10.98%)<br>205 |  |
| Viral upper respiratory tract infection                                                                           |                          |                            |  |

|                                                                                                         |                           |                           |  |
|---------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                        | 106 / 1377 (7.70%)<br>152 | 101 / 1384 (7.30%)<br>159 |  |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all) | 75 / 1377 (5.45%)<br>86   | 86 / 1384 (6.21%)<br>105  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 September 2014 | <p>Tiered weight-based start doses changed to fixed 70 mg TIW start dose: 120 and 350 mg dose steps removed. Dose algorithm adjusted to reflect results of pharmacometric modeling and simulation using the simplified dosing regimen. Dose cap lowered as additional modeling/simulation indicated this dose would be sufficient. Definition of excessive erythropoiesis simplified. Visit 1 changed to a phone call. Removed visits at Weeks 3, 5, and 7. Visits every 8 weeks (not 4 weeks) after Week 52. Visit window from <math>\pm 2</math> days to -4 days to 2 days. Priority order of secondary objectives changed. Rescue therapy objective prioritized before self-reported health status. Inclusion criteria: #3 reworded to clarify that qualifying eGFR was by central laboratory calculation; #5 and #6: Ferritin raised to <math>\geq 50</math> nanograms/mL and transferrin saturation raised to <math>\geq 15\%</math>. Exclusion criteria: #9 changed from Bosniak category II to IIF; #13 added "that is determined to be the principal cause of anemia". Removed "or their guardian/legal representative" for participant consent. Deleted IP discontinuation for thrombocytopenia or bleeding. Rescue medication: IV iron guidance adjusted to align with guidelines. Added recommendation for oral iron supplementation. Inclusion of statins text to ask Investigators to consider roxadustat-statin interactions and local prescribing information when deciding on appropriate statin dose for individual participants. Inclusion of text on phosphate binders. Efficacy analysis set: Participants were not to be censored 96 hours after their last dose in the OT+28 population; ITT analysis set for major adverse cardiovascular event (MACE) instead. ANCOVA changed to MMRM for efficacy analysis. Added: "In subjects who do not experience a MACE event, the time-to-event will be censored at the EOT visit for analyses based both on the safety analysis population and on FAS". Removed annual study discontinuation rate of 8.5% and changed estimated time from 1.5 years to 1.4 years.</p> |
| 31 August 2018    | <p>To harmonize D5740C00001 with other studies in the CKD-non-dialysis-dependent Phase 3 program, to serve as a pivotal study for confirming efficacy and safety and to facilitate assessment of pooled efficacy and safety data across the Phase 3 program, the following changes were implemented: Previous primary objective changed to primary safety objective (with CV safety analyses now being pooled across the study program). Addition of 2 primary efficacy objectives: one objective for the US FDA and one for the EU health authority. Previous primary objective text moved to new sub-section. Inclusion of text on pooled CV safety analyses and the pooled statistical analysis plan. Previous secondary objectives split out by objective type (efficacy and safety) and updated and new secondary objectives added. Study duration extended. Enrollment anticipated to occur over approximately a 3 year period. Text on sample size determination revised, including addition of text on sample size estimation for the primary efficacy objective. Study end date changed (extension of study into Q3 2018) to reflect a common end date across the Phase 3 studies when the required number of participants with adjudicated CV endpoints was anticipated. Additional criteria (participants requiring a third course of erythropoietin analogue rescue therapy, or those initiating dialysis who required erythropoietin analogue rescue therapy) for permanent discontinuation from the IP were added. Text added to state that hepcidin and hsCRP were to be analyzed from biomarker samples. Added definition of treatment emergent AE. FAS was renamed to the ITT and a new sub-section was added describing the new FAS. Changes were made to the criteria, treatment groups and censoring rules of the analysis sets. A new sub-section was added on participants who will not be included in any analysis set.</p>                                                                                                                                                                                    |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

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

|                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 participants were excluded from the analysis due to GCP violations or system technical issues (9 in the roxadustat group and 11 in the placebo group). Higher IP discontinuation was observed in placebo group versus in roxadustat group. |
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Notes: