



## Clinical trial results:

### Efficacy and tolerability of nicotinamide as add-on therapy compared to placebo in dialysis-dependent patients with hyperphosphatemia

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-000488-95 |
| Trial protocol           | DE PL AT HU    |
| Global end of trial date | 14 March 2017  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 20 October 2018 |
| First version publication date | 20 October 2018 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 6520-9961-04 |
|-----------------------|--------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | MEDICE Arzneimittel Pütter GmbH & Co. KG   |
| Sponsor organisation address | Kuhloweg 37, Iserlohn, Germany, 58638  |
| Public contact               | Medizinische Abteilung, MEDICE Arzneimittel Pütter GmbH & Co. KG, +49 2371937523, b.hellmann@medice.de |
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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                       | 09 July 2018  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 14 March 2017 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 14 March 2017 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Nicotinamide MR compared to placebo as an add-on therapy to approved individual phosphate binders in the long term reduction of elevated phosphate levels in haemodialysis patients

Protection of trial subjects:

The investigator should have discontinued the study medication for the following reasons:

- Lack of efficacy of the study medication even after rescue therapies
- Occurring of intolerable adverse effects even after dose reduction
- Platelet count less than 75/nl
- Creatine kinase increased  $\geq 5$  times the normal range
- Transaminase (AST, ALT) increased  $\geq 3$  times the normal range
- Use of medications/drugs not prescribed or allowed by the investigator and/or not permitted during the trial

- Onset of pregnancy
- Suspected relevant drug interaction(s)
- Subsequent ascertainment of non-fulfilment of the inclusion criteria or fulfilment of the exclusion criteria

- Continued trial participation unacceptable/unreasonable in the opinion of the investigator

Background therapy:

Unmodified phosphate binding therapy with one or two phosphate binders for at least 1 month prior to screening

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 15 August 2013 |
| 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 | Poland: 133  |
| Country: Number of subjects enrolled | Austria: 83  |
| Country: Number of subjects enrolled | Germany: 507 |
| Worldwide total number of subjects   | 723          |
| EEA total number of subjects         | 723          |

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)                      | 507 |
| From 65 to 84 years                       | 216 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Male and female patients >18 years on stable hemodialysis since at least 6 month were included at the study site

### Pre-assignment

Screening details:

1076 patients were screened in this clinical trial and of these 738 patients were randomised.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Efficacy and Safety Evaluation (overall period)     |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                             |
| Blinding used                | Double blind  |
| Roles blinded                | Investigator, Monitor, Data analyst, Carer, Subject |

Blinding implementation details:

Placebo capsules were identical to verum. Laboratory measurement of serum nicotinamide and its metabolite concentrations were transferred to data management not before unblinding.

### Arms

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

Arm description:

Verum

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Nicotinamide MR 250 mg capsules |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Capsule, hard                   |
| Routes of administration               | Oral use                        |

Dosage and administration details:

Dosage was titrated depending on serum phosphate concentrations between 1 and 6 capsules per day. Once daily intake at bed time or twice daily intake after wakeup and at bedtime.

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

Arm description:

Placebo

|  |                  |
|--|------------------|
| Arm type                               | Placebo          |
| Investigational medicinal product name | Placebo capsules |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule, hard    |
| Routes of administration               | Oral use         |

Dosage and administration details:

Dosage was titrated depending on serum phosphate concentrations between 1 and 6 capsules per day. Once daily intake at bed time or twice daily intake after wakeup and at bedtime.

| <b>Number of subjects in period 1</b> | Nicotinamide | Placebo |
|---------------------------------------|--------------|---------|
| Started                               | 540          | 183     |
| Completed                             | 402          | 144     |
| Not completed                         | 138          | 39      |
| Adverse event, serious fatal          | 24           | 9       |
| Consent withdrawn by subject          | 34           | 9       |
| Adverse event, non-fatal              | 27           | 3       |
| Renal transplantation                 | 40           | 16      |
| Lack of compliance                    | 3            | 2       |
| Lost to follow-up                     | 6            | -       |
| Protocol deviation                    | 4            | -       |

## Baseline characteristics

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Efficacy and Safety Evaluation |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values | Efficacy and Safety Evaluation | Total |  |
|------------------------|--------------------------------|-------|--|
| Number of subjects     | 723                            | 723   |  |
| Age categorical        |                                |       |  |
| Units: Subjects        |                                |       |  |
| Adults (18-64 years)   | 405                            | 405   |  |
| From 65-84 years       | 298                            | 298   |  |
| 85 years and over      | 20                             | 20    |  |
| Age continuous         |                                |       |  |
| Units: years           |                                |       |  |
| arithmetic mean        | 61.9                           |       |  |
| standard deviation     | ± 13.92                        | -     |  |
| Gender categorical     |                                |       |  |
| Units: Subjects        |                                |       |  |
| Female                 | 268                            | 268   |  |
| Male                   | 455                            | 455   |  |

### Subject analysis sets

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Safety Population |
|----------------------------|-------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The safety population includes all randomized patients who took the study medication at least once

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Intention to Treat Population |
|----------------------------|-------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Safety population with the exclusion of one legally impaired patient.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Per Protocol Population |
|----------------------------|-------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Patients of the Intention to treat with one of the following protocol deviations:

- Lack of compliance (less than 75% or more than 125% of the prescribed daily dose either during the whole study or in 2 consecutive study visits [week 0 to week 12 or between week 8 and week 12])
- Study medication was temporarily withdrawn for > 14 days between week 0 and week 8
- Retrospectively identified violation of inclusion/exclusion criteria at screening
- Incorrect study medication dispensed (randomization violated)
- Unblinding
- Confusion/mix up of provided study medication
- Drop-out (study medication withdrawn or entire study stopped) before week 12

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Completers population |
|----------------------------|-----------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All patients of the Per protocol population that neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing.

| <b>Reporting group values</b>         | Safety Population | Intention to Treat Population | Per Protocol Population |
|---------------------------------------|-------------------|-------------------------------|-------------------------|
| Number of subjects                    | 723               | 722                           | 439                     |
| Age categorical<br>Units: Subjects    |                   |                               |                         |
| Adults (18-64 years)                  | 405               |                               |                         |
| From 65-84 years                      | 298               |                               |                         |
| 85 years and over                     | 20                |                               |                         |
| Age continuous<br>Units: years        |                   |                               |                         |
| arithmetic mean                       | 61.9              | 61.8                          | 61.0                    |
| standard deviation                    | ± 13.92           | ± 13.92                       | ± 13.34                 |
| Gender categorical<br>Units: Subjects |                   |                               |                         |
| Female                                | 268               | 267                           | 151                     |
| Male                                  | 455               | 455                           | 288                     |

| <b>Reporting group values</b>         | Completers population |  |  |
|---------------------------------------|-----------------------|--|--|
| Number of subjects                    | 358                   |  |  |
| Age categorical<br>Units: Subjects    |                       |  |  |
| Adults (18-64 years)                  |                       |  |  |
| From 65-84 years                      |                       |  |  |
| 85 years and over                     |                       |  |  |
| Age continuous<br>Units: years        |                       |  |  |
| arithmetic mean                       | 61.1                  |  |  |
| standard deviation                    | ± 13.62               |  |  |
| Gender categorical<br>Units: Subjects |                       |  |  |
| Female                                | 123                   |  |  |
| Male                                  | 235                   |  |  |

## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Nicotinamide                  |
| Reporting group description:   |                               |
| Verum  |                               |
| Reporting group title  | Placebo                       |
| Reporting group description:   |                               |
| Placebo  |                               |
| Subject analysis set title   | Safety Population             |
| Subject analysis set type  | Safety analysis               |
| Subject analysis set description:  |                               |
| The safety population includes all randomized patients who took the study medication at least once   |                               |
| Subject analysis set title   | Intention to Treat Population |
| Subject analysis set type  | Intention-to-treat            |
| Subject analysis set description:  |                               |
| Safety population with the exclusion of one legally impaired patient.  |                               |
| Subject analysis set title   | Per Protocol Population       |
| Subject analysis set type  | Per protocol                  |
| Subject analysis set description:  |                               |
| Patients of the Intention to treat with one of the following protocol deviations:  |                               |
| <ul style="list-style-type: none"><li>• Lack of compliance (less than 75% or more than 125% of the prescribed daily dose either during the whole study or in 2 consecutive study visits [week 0 to week 12 or between week 8 and week 12])</li><li>• Study medication was temporarily withdrawn for &gt; 14 days between week 0 and week 8</li><li>• Retrospectively identified violation of inclusion/exclusion criteria at screening</li><li>• Incorrect study medication dispensed (randomization violated)</li><li>• Unblinding</li><li>• Confusion/mix up of provided study medication</li><li>• Drop-out (study medication withdrawn or entire study stopped) before week 12</li></ul> |                               |
| Subject analysis set title   | Completers population         |
| Subject analysis set type  | Sub-group analysis            |
| Subject analysis set description:  |                               |
| All patients of the Per protocol population that neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing.  |                               |

### Primary: Serum Phosphate (Intention to Treat Population)

|  |   |
|--|---|
| End point title  | Serum Phosphate (Intention to Treat Population) |
| End point description:   |   |
| The primary criterion of this study was the serum phosphate concentration in mg/dL at W12 for the ITT population. The analysis was based on a linear mixed model to also address the stratification factors of the randomization. The factors/covariates study medication group, study site, individual additional phosphate binder (phosphate binder containing calcium, lanthanum carbonate and aluminum, and other phosphate binders) and initial value of phosphate (screening) were considered. The study medication group was included as a fixed effect; the study site was modelled as random effect (random intercept). The initial value of phosphate and the individual additional phosphate binder(s) were included as fixed effect covariates. Interactions were not considered in the primary model. The claim of superiority was based on a two-sided p-value related to the Wald-type test statistic for the treatment effect applying a two-sided significance concentration of 2.5%. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| 12 weeks   |   |



|                                      |                     |                     |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>              | Nicotinamide        | Placebo             |  |  |
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 499                 | 174                 |  |  |
| Units: mg/dL                         |                     |                     |  |  |
| arithmetic mean (standard deviation) | 5.36 ( $\pm$ 1.382) | 5.88 ( $\pm$ 1.319) |  |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>   | Primary Endpoint Serum Phosphate |
| Statistical analysis description:   |                                  |
| The analysis was based on a linear mixed model to also address the stratification factors of the randomization. |                                  |
| Comparison groups   | Nicotinamide v Placebo           |
| Number of subjects included in analysis   | 673                              |
| Analysis specification  | Pre-specified                    |
| Analysis type   | superiority                      |
| P-value   | < 0.001                          |
| Method  | Kruskal-wallis                   |
| Parameter estimate  | Mean difference (final values)   |
| Point estimate  | -0.506                           |
| Confidence interval   |                                  |
| level   | 95 %                             |
| sides   | 2-sided                          |
| lower limit   | -0.723                           |
| upper limit   | -0.289                           |

## Secondary: Serum Phosphate (Per Protocol Population)

|                        |   |
|------------------------|---|
| End point title        | Serum Phosphate (Per Protocol Population) |
| End point description: |   |
| End point type         | Secondary                                 |
| End point timeframe:   |   |
| 12 weeks               |   |

| End point values                     | Nicotinamide        | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 320                 | 119                 |  |  |
| Units: mg/dL                         |                     |                     |  |  |
| arithmetic mean (standard deviation) | 5.25 ( $\pm$ 1.217) | 5.84 ( $\pm$ 1.360) |  |  |

## Statistical analyses

| Statistical analysis title              | Secondary Endpoint Serum Phosphat PP Population |
|---|---|
| Comparison groups                       | Nicotinamide v Placebo                          |
| Number of subjects included in analysis | 439   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | < 0.001   |
| Method                                  | Kruskal-wallis                                  |
| Parameter estimate                      | Mean difference (final values)                  |
| Point estimate                          | -0.61   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.85   |
| upper limit                             | -0.37   |

## Secondary: Serum Phosphate (Completer Population)

|                        |  |
|------------------------|--|
| End point title        | Serum Phosphate (Completer Population)   |
| End point description: | The completers population consisted of patients who neither terminated study medication intake permanently nor study participation prematurely (i.e. before week 52) and who had a record for serum phosphate at week 52 irrespective of whether the phosphate value at screening was missing. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| 52 weeks               |  |

| End point values                     | Nicotinamide        | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 251                 | 107                 |  |  |
| Units: mg/dL                         |                     |                     |  |  |
| arithmetic mean (standard deviation) | 5.41 ( $\pm$ 1.412) | 5.76 ( $\pm$ 1.513) |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Secondary Endpoint Serum Phosphat Completers Popul |
| Comparison groups                       | Placebo v Nicotinamide                             |
| Number of subjects included in analysis | 358  |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | superiority  |
| P-value                                 | = 0.0309   |
| Method                                  | Kruskal-wallis                                     |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Screening examination until week 52. Adverse events occurring within 4 weeks after last intake of study medication were additionally recorded.

Adverse event reporting additional description:

Adverse events were registred continuously during the clinical trial at each study visit. All adverse events were recorded irregardless wether the patient was under study medication or it was terminated.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Nicotinamide |
|-----------------------|--------------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events  | Nicotinamide       | Placebo           |  |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                    |                   |  |
| subjects affected / exposed   | 274 / 540 (50.74%) | 93 / 183 (50.82%) |  |
| number of deaths (all causes)                                       | 32                 | 11                |  |
| number of deaths resulting from adverse events                      | 32                 | 11                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                   |  |
| Basal cell carcinoma  |                    |                   |  |
| subjects affected / exposed   | 2 / 540 (0.37%)    | 0 / 183 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 2              | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0             |  |
| Bladder neoplasm  |                    |                   |  |
| subjects affected / exposed   | 1 / 540 (0.19%)    | 0 / 183 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0             |  |
| Breast cancer   |                    |                   |  |
| subjects affected / exposed   | 1 / 540 (0.19%)    | 0 / 183 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 0             |  |
| Carcinoid tumour pulmonary  |                    |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Colon adenoma                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Eosinophilic leukaemia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lung carcinoma cell type unspecified stage III  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lung neoplasm                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant neoplasm papilla of Vater             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to liver                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to peritoneum                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to spine                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostatic adenoma                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal neoplasm                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin cancer                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Air embolism                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial occlusive disease                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic macroangiopathy                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic microangiopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Granulomatosis with polyangiitis                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 8 / 540 (1.48%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                             |                 |                 |  |
| subjects affected / exposed                     | 8 / 540 (1.48%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemia                                       |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (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                     | 14 / 540 (2.59%) | 3 / 183 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 18           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Peripheral artery stenosis                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Peripheral ischaemia                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Shock haemorrhagic                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Subclavian vein stenosis                        |                  |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombophlebitis                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vasculitis                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Venous stenosis                                 |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Analgesic intervention supportive therapy       |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriovenous fistula operation                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriovenous shunt operation                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Catheter removal                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central venous catheterisation                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystectomy                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Debridement                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot amputation                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric stapling                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip arthroplasty                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hysterectomy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mechanical ventilation                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrectomy                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parathyroidectomy                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery stent insertion               |                 |                 |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Polypectomy  |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Removal of renal transplant                          |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Renal transplant                                     |                  |                  |  |
| subjects affected / exposed                          | 40 / 540 (7.41%) | 17 / 183 (9.29%) |  |
| occurrences causally related to treatment / all      | 0 / 40           | 0 / 17           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Resuscitation  |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Stent placement                                      |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Tracheal fistula repair                              |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Adverse drug reaction                                |                  |                  |  |
| subjects affected / exposed                          | 1 / 540 (0.19%)  | 0 / 183 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Asthenia   |                  |                  |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac death                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Chest pain                                      |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chills  |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Condition aggravated                            |                  |                 |  |
| subjects affected / exposed                     | 13 / 540 (2.41%) | 4 / 183 (2.19%) |  |
| occurrences causally related to treatment / all | 3 / 14           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Death   |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1           |  |
| Device malfunction                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fatigue   |                  |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| General physical health deterioration           |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic cyst                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired healing                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inflammation                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Necrosis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain  |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 3 / 183 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sudden cardiac death                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Sudden death                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Immune system disorders                         |                 |                 |  |
| Sarcoidosis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transplant rejection                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Social circumstances                            |                 |                 |  |
| Patient uncooperative                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Breast inflammation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometrial hyperplasia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Vaginal prolapse                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (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 |                  |                 |  |
| Chronic obstructive pulmonary disease           |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dyspnoea  |                  |                 |  |
| subjects affected / exposed                     | 10 / 540 (1.85%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Epistaxis                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypoventilation                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pleural effusion                                |                  |                 |  |
| subjects affected / exposed                     | 7 / 540 (1.30%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 11           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pleurisy  |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia aspiration                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| Pulmonary congestion                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary embolism                              |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pulmonary hypertension                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary mass                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary oedema                                |                  |                 |  |
| subjects affected / exposed                     | 12 / 540 (2.22%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| Respiratory distress                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (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                     | 0 / 540 (0.00%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Sleep apnoea syndrome                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Psychiatric disorders                           |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Agitation                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alcohol abuse                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disorientation                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organic brain syndrome                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sleep disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholangitis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocholecystitis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Antineutrophil cytoplasmic antibody positive    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriogram coronary                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biopsy prostate                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood albumin abnormal                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Blood glucose increased                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Body temperature increased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| C-reactive protein abnormal                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| C-reactive protein increased                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Electrocardiogram abnormal                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial necrosis marker increased            |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Alcohol poisoning                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Animal scratch                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriovenous fistula aneurysm                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriovenous fistula site haemorrhage          |                 |                 |  |
| subjects affected / exposed                     | 6 / 540 (1.11%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain contusion                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cartilage injury                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cervical vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clavicle fracture                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Concussion                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 3 / 183 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dialysis related complication                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endotracheal intubation complication            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Face injury                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Facial bones fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 540 (0.93%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fat embolism                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemodialysis complication                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inflammation of wound                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint dislocation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laceration                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament sprain                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mechanical ventilation complication             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meniscus injury                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Overdose  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural complication                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 3 / 183 (1.64%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt aneurysm                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt stenosis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt thrombosis                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin abrasion                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulna fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular access complication                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular graft complication                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Congenital cystic kidney disease                |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Aortic valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic valve stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 6 / 540 (1.11%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 7 / 540 (1.30%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Congestive cardiomyopathy                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 7 / 540 (1.30%) | 4 / 183 (2.19%) |  |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve stenosis                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 6 / 540 (1.11%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachyarrhythmia                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Aphasia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arachnoid cyst                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral circulatory failure                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular disorder                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clonus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysarthria                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial paralysis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intercostal neuralgia                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lacunar infarction                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sciatica  |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sedation  |                  |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Seizure   |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Syncope   |                  |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%)  | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Agranulocytosis                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anaemia   |                  |                 |  |
| subjects affected / exposed                     | 13 / 540 (2.41%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 21           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Anaemia macrocytic                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eosinophilia                                    |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic anaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Iron deficiency anaemia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukocytosis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphadenopathy                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Normochromic normocytic anaemia                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Age-related macular degeneration<br>subjects affected / exposed | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Cataract<br>subjects affected / exposed                         | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Diabetic retinopathy<br>subjects affected / exposed             | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Eyelid haematoma<br>subjects affected / exposed                 | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Glaucoma<br>subjects affected / exposed                         | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Retinal detachment<br>subjects affected / exposed               | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                                      |                 |                 |  |
| Abdominal discomfort<br>subjects affected / exposed             | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           |  |
| Abdominal pain<br>subjects affected / exposed                   | 4 / 540 (0.74%) | 3 / 183 (1.64%) |  |
| occurrences causally related to<br>treatment / all              | 2 / 5           | 0 / 3           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 1           |  |
| Abdominal pain upper  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal erosion                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bowel movement irregularity                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic gastritis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis microscopic                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal haemorrhagic            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal polyp                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flatulence                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric polyps                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis haemorrhagic                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal angiodysplasia                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 7 / 540 (1.30%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 2 / 7           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal mucosa hyperaemia              |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal pain                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal polyp haemorrhage              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic erosive gastritis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoidal haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal haemorrhage                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 540 (1.11%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Decubitus ulcer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin lesion                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin necrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| 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                     | 3 / 540 (0.56%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Azotaemia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Calculus urethral                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic kidney disease                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| IgA nephropathy                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Goitre  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperparathyroidism                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperparathyroidism secondary                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondritis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondropathy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loose body in joint                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteitis  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 6 / 540 (1.11%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthropathy                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal column stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Synovial cyst                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>              |                 |                 |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acarodermatitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis perforated                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| 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                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial disease carrier                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| 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 / 540 (1.67%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 1 / 10          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carbuncle                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic tonsillitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Diabetic gangrene                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis brain stem                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gangrene  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis clostridial                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastroenteritis norovirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal candidiasis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster meningoencephalitis               |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Herpes zoster meningomyelitis                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Infected cyst                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (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                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infection                                       |                  |                 |  |
| subjects affected / exposed                     | 11 / 540 (2.04%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Influenza                                       |                  |                 |  |
| subjects affected / exposed                     | 4 / 540 (0.74%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intervertebral discitis                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Listeriosis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Liver abscess                                   |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lyme disease                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mastoiditis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Meningoencephalitis herpetic                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Oropharyngeal candidiasis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pathogen resistance                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Peritonitis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Peritonitis bacterial                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (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                     | 29 / 540 (5.37%) | 8 / 183 (4.37%) |  |
| occurrences causally related to treatment / all | 0 / 29           | 0 / 10          |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3           |  |
| Pneumonia influenzal                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia pneumococcal                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Postoperative wound infection                   |                  |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis                                  |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyelonephritis chronic                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory tract infection                     |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sepsis  |                  |                 |  |
| subjects affected / exposed                     | 11 / 540 (2.04%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0           |  |
| Septic shock                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Shunt infection                                 |                  |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal bacteraemia                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal infection                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%)  | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal sepsis                           |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 540 (0.93%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 540 (0.37%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheobronchitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Uterine infection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (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                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 540 (0.37%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |  |
| <b>Dehydration</b>                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Diabetic ketoacidosis</b>                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 540 (0.00%) | 1 / 183 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Fluid overload</b>                           |                 |                 |  |
| subjects affected / exposed                     | 5 / 540 (0.93%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| <b>Hypercalcaemia</b>                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hyperkalaemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 2 / 183 (1.09%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypervolaemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 540 (0.56%) | 0 / 183 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypoglycaemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 540 (0.19%) | 1 / 183 (0.55%) |  |
| 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>                     | Nicotinamide       | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 511 / 540 (94.63%) | 159 / 183 (86.89%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed                           | 82 / 540 (15.19%)  | 22 / 183 (12.02%)  |  |
| occurrences (all)                                     | 118                | 29                 |  |
| Hypotension   |                    |                    |  |
| subjects affected / exposed                           | 28 / 540 (5.19%)   | 12 / 183 (6.56%)   |  |
| occurrences (all)                                     | 39                 | 16                 |  |
| Surgical and medical procedures                       |                    |                    |  |
| Renal transplant                                      |                    |                    |  |
| subjects affected / exposed                           | 40 / 540 (7.41%)   | 17 / 183 (9.29%)   |  |
| occurrences (all)                                     | 40                 | 17                 |  |
| Nervous system disorders                              |                    |                    |  |
| Headache  |                    |                    |  |
| subjects affected / exposed                           | 53 / 540 (9.81%)   | 13 / 183 (7.10%)   |  |
| occurrences (all)                                     | 73                 | 15                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Condition aggravated                                  |                    |                    |  |
| subjects affected / exposed                           | 30 / 540 (5.56%)   | 8 / 183 (4.37%)    |  |
| occurrences (all)                                     | 35                 | 9                  |  |
| Blood and lymphatic system disorders                  |                    |                    |  |
| Anemia  |                    |                    |  |
| subjects affected / exposed                           | 60 / 540 (11.11%)  | 13 / 183 (7.10%)   |  |
| occurrences (all)                                     | 90                 | 15                 |  |
| Thrombocytopenia                                      |                    |                    |  |
| subjects affected / exposed                           | 28 / 540 (5.19%)   | 2 / 183 (1.09%)    |  |
| occurrences (all)                                     | 39                 | 2                  |  |
| Gastrointestinal disorders                            |                    |                    |  |
| Diarrhoea   |                    |                    |  |
| subjects affected / exposed                           | 240 / 540 (44.44%) | 51 / 183 (27.87%)  |  |
| occurrences (all)                                     | 451                | 71                 |  |
| Nausea  |                    |                    |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 79 / 540 (14.63%) | 20 / 183 (10.93%) |  |
| occurrences (all)                               | 104               | 27                |  |
| Vomiting  |                   |                   |  |
| subjects affected / exposed                     | 62 / 540 (11.48%) | 10 / 183 (5.46%)  |  |
| occurrences (all)                               | 79                | 16                |  |
| Abdominal pain                                  |                   |                   |  |
| subjects affected / exposed                     | 23 / 540 (4.26%)  | 11 / 183 (6.01%)  |  |
| occurrences (all)                               | 26                | 12                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 41 / 540 (7.59%)  | 9 / 183 (4.92%)   |  |
| occurrences (all)                               | 53                | 10                |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 30 / 540 (5.56%)  | 4 / 183 (2.19%)   |  |
| occurrences (all)                               | 41                | 6                 |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Pruritus  |                   |                   |  |
| subjects affected / exposed                     | 74 / 540 (13.70%) | 12 / 183 (6.56%)  |  |
| occurrences (all)                               | 97                | 12                |  |
| Psychiatric disorders                           |                   |                   |  |
| Sleep disorder                                  |                   |                   |  |
| subjects affected / exposed                     | 32 / 540 (5.93%)  | 9 / 183 (4.92%)   |  |
| occurrences (all)                               | 39                | 9                 |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Muscle spasms                                   |                   |                   |  |
| subjects affected / exposed                     | 48 / 540 (8.89%)  | 18 / 183 (9.84%)  |  |
| occurrences (all)                               | 82                | 43                |  |
| Arthralgia                                      |                   |                   |  |
| subjects affected / exposed                     | 23 / 540 (4.26%)  | 13 / 183 (7.10%)  |  |
| occurrences (all)                               | 26                | 15                |  |
| Infections and infestations                     |                   |                   |  |
| Nasopharyngitis                                 |                   |                   |  |
| subjects affected / exposed                     | 97 / 540 (17.96%) | 26 / 183 (14.21%) |  |
| occurrences (all)                               | 133               | 41                |  |
| Bronchitis                                      |                   |                   |  |



|                                    |                   |                  |  |
|------------------------------------|-------------------|------------------|--|
| subjects affected / exposed        | 55 / 540 (10.19%) | 13 / 183 (7.10%) |  |
| occurrences (all)                  | 66                | 17               |  |
| Pneumonia                          |                   |                  |  |
| subjects affected / exposed        | 35 / 540 (6.48%)  | 9 / 183 (4.92%)  |  |
| occurrences (all)                  | 37                | 11               |  |
| Urinary tract infection            |                   |                  |  |
| subjects affected / exposed        | 29 / 540 (5.37%)  | 8 / 183 (4.37%)  |  |
| occurrences (all)                  | 34                | 8                |  |
| Herpes zoster                      |                   |                  |  |
| subjects affected / exposed        | 29 / 540 (5.37%)  | 0 / 183 (0.00%)  |  |
| occurrences (all)                  | 31                | 0                |  |
| Metabolism and nutrition disorders |                   |                  |  |
| Decreased appetite                 |                   |                  |  |
| subjects affected / exposed        | 36 / 540 (6.67%)  | 10 / 183 (5.46%) |  |
| occurrences (all)                  | 46                | 10               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 22 October 2013  | Change in Prohibited Comedications: Magnesium intake should be generally allowed.  |
| 22 December 2013 | Change in inclusion and exclusion criteria: Inclusionrange of phosphate concentration was extendet to < 2.42 mmol/l (7.5 mg/dl) and > 1.45 mmol/l (4.5 mg/dl). Intake of concomitent medication nicontic acid was allowed up to a dose of 150 mg / week. |
| 10 June 2014     | Change in inclusion and exclusion criteria: Permission of a second phosphat binder. Inclusionrange of phosphate concentration was extendet to < 2.80 mmol/l (8.7 mg/dl) and > 1.45 mmol/l (4.5 mg/dl).   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported