

**Clinical trial results:****A Multicenter, International, Phase 3, Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy, Safety, and Tolerability of Daily Oral Dosing of Tafamidis Meglumine (PF-06291826) 20 mg or 80 mg in Comparison to Placebo in Subjects Diagnosed With Transthyretin Cardiomyopathy (TTR-CM)****Summary**

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2012-002465-35          |
| Trial protocol           | GB IT ES DE SE CZ NL BE |
| Global end of trial date | 07 February 2018        |

**Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 01 May 2019      |
| First version publication date | 16 February 2019 |
| Version creation reason        |                  |

**Trial information****Trial identification**

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | B3461028 |
|-----------------------|----------|

**Additional study identifiers**

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | -  |
| ClinicalTrials.gov id (NCT number) | NCT01994889                                    |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | ATTR-ACT: Other Identifier: Alias Study Number |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Pfizer Inc.  |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017   |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

**Paediatric regulatory details**

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

Notes:

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**Results analysis stage**

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 28 August 2018 |
| Is this the analysis of the primary completion data? | No             |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 07 February 2018 |
| Was the trial ended prematurely? | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

To assess the efficacy of an oral dose of 20 milligrams (mg) or 80 mg tafamidis meglumine soft-gel capsules based on all-cause mortality and on frequency of cardiovascular-related hospitalizations as well as to assess safety and tolerability in comparison to placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 09 December 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 2         |
| Country: Number of subjects enrolled | Brazil: 2          |
| Country: Number of subjects enrolled | Canada: 1          |
| Country: Number of subjects enrolled | Czech Republic: 8  |
| Country: Number of subjects enrolled | France: 28         |
| Country: Number of subjects enrolled | Germany: 49        |
| Country: Number of subjects enrolled | Italy: 29          |
| Country: Number of subjects enrolled | Japan: 17          |
| Country: Number of subjects enrolled | Netherlands: 7     |
| Country: Number of subjects enrolled | Spain: 9           |
| Country: Number of subjects enrolled | Sweden: 6          |
| Country: Number of subjects enrolled | United Kingdom: 4  |
| Country: Number of subjects enrolled | United States: 279 |
| Worldwide total number of subjects   | 441                |
| EEA total number of subjects         | 142                |

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)                      | 42  |
| From 65 to 84 years                       | 377 |
| 85 years and over                         | 22  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Pooled analysis of the tafamidis treatment groups 20 mg and 80 mg was performed in comparison to placebo group.

### Period 1

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

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Tafamidis 20 mg |

Arm description:

Subjects with variant transthyretin cardiomyopathy (TTR-CM) genotype or wild-type TTRCM genotype received one tafamidis 20 milligram (mg) capsule + 3 placebo capsules (matched to tafamidis) orally once daily for 30 months.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Tafamidis meglumine |
| Investigational medicinal product code | PF-06291826         |
| Other name                             |                     |
| Pharmaceutical forms                   | Capsule, soft       |
| Routes of administration               | Oral use            |

Dosage and administration details:

One tafamidis 20 mg capsule + 3 placebo capsules (matched to tafamidis), orally once daily for 30 months.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Tafamidis 80 mg |
|------------------|-----------------|

Arm description:

Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received tafamidis 80 mg (4 capsules of 20 mg each) orally once daily for 30 months.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Tafamidis meglumine |
| Investigational medicinal product code | PF-06291826         |
| Other name                             |                     |
| Pharmaceutical forms                   | Capsule, soft       |
| Routes of administration               | Oral use            |

Dosage and administration details:

Tafamidis 80 mg (4 capsules of 20 mg each), orally once daily for 30 months.

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

Arm description:

Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received 4 placebo capsules matched to tafamidis orally once daily for 30 months.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |               |
|--|---------------|
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Four placebo capsules (matched to tafamidis), orally once daily for 30 months.

| <b>Number of subjects in period 1</b> | Tafamidis 20 mg | Tafamidis 80 mg | Placebo |
|---------------------------------------|-----------------|-----------------|---------|
| Started                               | 88              | 176             | 177     |
| Completed                             | 60              | 113             | 85      |
| Not completed                         | 28              | 63              | 92      |
| Adverse event, serious fatal          | 5               | 8               | 7       |
| Organ Transplantation                 | 1               | 5               | 5       |
| Adverse event, non-fatal              | -               | 1               | 1       |
| Death                                 | 14              | 25              | 38      |
| Adverse event, serious non fatal      | -               | 3               | 3       |
| No longer willing to participate      | 8               | 17              | 37      |
| Cardiac Device Implantation           | -               | 2               | -       |
| Lost to follow-up                     | -               | 1               | -       |
| Protocol deviation                    | -               | 1               | 1       |

## Baseline characteristics

### Reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Tafamidis 20 mg |
| Reporting group description:<br>Subjects with variant transthyretin cardiomyopathy (TTR-CM) genotype or wild-type TTRCM genotype received one tafamidis 20 milligram (mg) capsule + 3 placebo capsules (matched to tafamidis) orally once daily for 30 months. |                 |
| Reporting group title  | Tafamidis 80 mg |
| Reporting group description:<br>Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received tafamidis 80 mg (4 capsules of 20 mg each) orally once daily for 30 months.  |                 |
| Reporting group title  | Placebo         |
| Reporting group description:<br>Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received 4 placebo capsules matched to tafamidis orally once daily for 30 months.   |                 |

| Reporting group values  | Tafamidis 20 mg | Tafamidis 80 mg | Placebo |
|---|-----------------|-----------------|---------|
| Number of subjects  | 88              | 176             | 177     |
| Age categorical   |                 |                 |         |
| The intent-to-treat (ITT) analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death). |                 |                 |         |
| Units: Subjects   |                 |                 |         |
| Adults (18-64 years)  | 11              | 16              | 15      |
| From 65-84 years  | 74              | 148             | 155     |
| 85 years and over   | 3               | 12              | 7       |
| Age Continuous  |                 |                 |         |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |                 |                 |         |
| Units: years  |                 |                 |         |
| arithmetic mean   | 73.3            | 75.2            | 74.1    |
| standard deviation  | ± 7.07          | ± 7.24          | ± 6.69  |
| Sex: Female, Male   |                 |                 |         |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |                 |                 |         |
| Units: Subjects   |                 |                 |         |
| Female  | 5               | 18              | 20      |
| Male  | 83              | 158             | 157     |
| Race (NIH/OMB)  |                 |                 |         |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |                 |                 |         |
| Units: Subjects   |                 |                 |         |
| American Indian or Alaska Native  | 0               | 0               | 0       |
| Asian   | 2               | 11              | 5       |
| Native Hawaiian or Other Pacific Islander   | 0               | 0               | 0       |
| Black or African American   | 11              | 26              | 26      |
| White   | 75              | 136             | 146     |
| More than one race  | 0               | 0               | 0       |

|   |    |     |     |
|---|----|-----|-----|
| Unknown or Not Reported   | 0  | 3   | 0   |
| Ethnicity (NIH/OMB)   |    |     |     |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death). |    |     |     |
| Units: Subjects   |    |     |     |
| Hispanic or Latino  | 3  | 4   | 7   |
| Not Hispanic or Latino  | 84 | 171 | 170 |
| Unknown or Not Reported   | 1  | 1   | 0   |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 441   |  |  |
| Age categorical   |       |  |  |
| The intent-to-treat (ITT) analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death). |       |  |  |
| Units: Subjects   |       |  |  |
| Adults (18-64 years)  | 42    |  |  |
| From 65-84 years  | 377   |  |  |
| 85 years and over   | 22    |  |  |
| Age Continuous  |       |  |  |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |       |  |  |
| Units: years  |       |  |  |
| arithmetic mean   |       |  |  |
| standard deviation  | -     |  |  |
| Sex: Female, Male   |       |  |  |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |       |  |  |
| Units: Subjects   |       |  |  |
| Female  | 43    |  |  |
| Male  | 398   |  |  |
| Race (NIH/OMB)  |       |  |  |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |       |  |  |
| Units: Subjects   |       |  |  |
| American Indian or Alaska Native  | 0     |  |  |
| Asian   | 18    |  |  |
| Native Hawaiian or Other Pacific Islander   | 0     |  |  |
| Black or African American   | 63    |  |  |
| White   | 357   |  |  |
| More than one race  | 0     |  |  |
| Unknown or Not Reported   | 3     |  |  |
| Ethnicity (NIH/OMB)   |       |  |  |
| The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation ( post baseline hospitalization, study visit, or date of death).                   |       |  |  |
| Units: Subjects   |       |  |  |
| Hispanic or Latino  | 14    |  |  |
| Not Hispanic or Latino  | 425   |  |  |
| Unknown or Not Reported   | 2     |  |  |





## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Tafamidis 20 mg    |
| Reporting group description:<br>Subjects with variant transthyretin cardiomyopathy (TTR-CM) genotype or wild-type TTRCM genotype received one tafamidis 20 milligram (mg) capsule + 3 placebo capsules (matched to tafamidis) orally once daily for 30 months. |                    |
| Reporting group title  | Tafamidis 80 mg    |
| Reporting group description:<br>Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received tafamidis 80 mg (4 capsules of 20 mg each) orally once daily for 30 months.  |                    |
| Reporting group title  | Placebo            |
| Reporting group description:<br>Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received 4 placebo capsules matched to tafamidis orally once daily for 30 months.   |                    |
| Subject analysis set title   | Tafamidis          |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:<br>Subjects with variant TTR-CM genotype or wild-type TTR-CM genotype received one tafamidis 20 mg + 3 placebo capsules (matched to tafamidis) or 80 mg (4 capsules of 20 mg each) capsule orally once daily for 30 months.  |                    |

### Primary: Hierarchical Combination of All-Cause Mortality and Frequency of Cardiovascular (CV)-Related Hospitalizations

|   |  |
|---|--|
| End point title   | Hierarchical Combination of All-Cause Mortality and Frequency of Cardiovascular (CV)-Related Hospitalizations <sup>[1]</sup> |
| End point description:<br>All-cause mortality and frequency of CV hospitalization were analyzed using Finkelstein-Schoenfeld method, which combines in a hierarchical fashion using all-cause mortality first. The method compares every subject with every other subject within strata, assigning a +1 to the "better" subject and a -1 to the "worse" subject and 0 if they are "tied". Subjects who discontinued for transplantation (heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the same manner as death. 'Win' represents a subject doing better based on hierarchical comparison. The reported unit is the total 'wins' for each treatment group from performing such a hierarchical comparison across all 4 strata in the study. Analysis done on ITT analysis set. Pre-specified intent of study was to compare results between tafamidis with placebo, irrespective of tafamidis doses. Analysis based on pooled dose groups, as per study protocol. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline up to Month 30   |  |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| End point values            | Placebo         | Tafamidis            |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 177             | 264                  |  |  |
| Units: wins                 |                 |                      |  |  |
| number (not applicable)     | 5071            | 8595                 |  |  |

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Tafamidis Vs. Placebo         |
| Comparison groups                       | Placebo v Tafamidis           |
| Number of subjects included in analysis | 441                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.0006                      |
| Method                                  | Finkelstein-Schoenfeld Method |

## Secondary: All-Cause Mortality

|                 |                                    |
|-----------------|------------------------------------|
| End point title | All-Cause Mortality <sup>[2]</sup> |
|-----------------|------------------------------------|

End point description:

Number of deaths during the study due to any cause was analyzed. Subjects who discontinued for transplantation (heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device were handled in the same manner as death. The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation (post baseline hospitalization, study visit, or date of death). The pre-specified intent of this study was to compare the results between tafamidis with placebo, irrespective of the tafamidis doses. Therefore, this analysis was based on the pooled dose groups, as per the study protocol.

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

End point timeframe:

Baseline up to Month 30

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

|                                   |                 |                      |  |  |
|-----------------------------------|-----------------|----------------------|--|--|
| <b>End point values</b>           | Placebo         | Tafamidis            |  |  |
| Subject group type                | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed       | 177             | 264                  |  |  |
| Units: subjects                   |                 |                      |  |  |
| Deaths (all causes)               | 72              | 69                   |  |  |
| Heart transplants                 | 4               | 7                    |  |  |
| Cardiac Mechanical Assist Devices | 0               | 2                    |  |  |

## Statistical analyses

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Tafamidis Vs. Placebo |
|-----------------------------------|-----------------------|

Statistical analysis description:

Hazard ratio from a Cox proportional hazards model with treatment, TTR genotype (variant and wild-type) and New York Heart Association (NYHA) baseline classification (NYHA Classes I and II combined and NYHA Class III) in the model.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Placebo v Tafamidis |
|-------------------|---------------------|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 441                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0259                       |
| Method                                  | Cox proportional hazards model |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.698                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.508                          |
| upper limit                             | 0.958                          |

## Secondary: Frequency of Cardiovascular-Related Hospitalizations

|                 |   |
|-----------------|---|
| End point title | Frequency of Cardiovascular-Related Hospitalizations <sup>[3]</sup> |
|-----------------|---|

End point description:

CV related hospitalizations per year is calculated as subject's number of CV related hospitalizations upon duration on study in years. The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation (post baseline hospitalization, study visit, or date of death). The pre-specified intent of this study was to compare the results between tafamidis with placebo, irrespective of the tafamidis doses. Therefore, this analysis was based on the pooled dose groups, as per the study protocol.

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

End point timeframe:

Baseline to Month 30

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| End point values                     | Placebo          | Tafamidis            |  |  |
|--------------------------------------|------------------|----------------------|--|--|
| Subject group type                   | Reporting group  | Subject analysis set |  |  |
| Number of subjects analysed          | 177              | 264                  |  |  |
| Units: CV hospitalization per year   |                  |                      |  |  |
| arithmetic mean (standard deviation) | 0.884 (± 1.2032) | 0.999 (± 2.2777)     |  |  |

## Statistical analyses

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | Tafamidis Vs. Placebo |
| Comparison groups          | Placebo v Tafamidis   |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 441                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.0001 <sup>[4]</sup>     |
| Method                                  | Poisson regression analysis |
| Parameter estimate                      | Risk ratio (RR)             |
| Point estimate                          | 0.6761                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.5639                      |
| upper limit                             | 0.8107                      |

Notes:

[4] - Poisson regression analysis with treatment, TTR Genotype, NYHA Baseline classification, treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors adjusted for treatment duration.

## Secondary: Change From Baseline in the Total Distance Walked During 6 Minute Walk Test (6MWT) at Month 30

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in the Total Distance Walked During 6 Minute Walk Test (6MWT) at Month 30 <sup>[5]</sup> |
|-----------------|---|

End point description:

6MWT is the total distance that a subject could walk in 6 minutes. Subjects were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation (post baseline hospitalization, study visit, or date of death). The pre-specified intent of this study was to compare the results between tafamidis with placebo, irrespective of the tafamidis doses. Therefore, this analysis was based on the pooled dose groups, as per the study protocol. Here, 'n' = Subjects evaluable for this end point at specified time points.

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

End point timeframe:

Baseline, Month 30

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| End point values                     | Placebo            | Tafamidis            |  |  |
|--------------------------------------|--------------------|----------------------|--|--|
| Subject group type                   | Reporting group    | Subject analysis set |  |  |
| Number of subjects analysed          | 177                | 264                  |  |  |
| Units: meters                        |                    |                      |  |  |
| arithmetic mean (standard deviation) |                    |                      |  |  |
| Baseline (n=177, 264)                | 353.26 (± 125.983) | 350.55 (± 121.296)   |  |  |
| Change at Month 30 (n=70, 155)       | -89.67 (± 105.159) | -30.46 (± 87.886)    |  |  |

## Statistical analyses

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | Tafamidis Vs. Placebo |
|----------------------------|-----------------------|

Statistical analysis description:

L.S. means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and

subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit by treatment interaction, as fixed effects and baseline score as covariate.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | Placebo v Tafamidis                  |
| Number of subjects included in analysis | 441                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | < 0.0001                             |
| Method                                  | Mixed Model Repeated Measures ANCOVA |
| Parameter estimate                      | Least Square Mean Difference         |
| Point estimate                          | 75.68                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 57.56                                |
| upper limit                             | 93.8                                 |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 9.236                                |

## Secondary: Change from Baseline in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) at Month 30

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) at Month 30 <sup>[6]</sup> |
|-----------------|---|

End point description:

KCCQ: 23-item subject-completed questionnaire that assesses health status and health-related quality of life in subjects with heart failure. Eight domain scores were calculated: Physical limitation, Social limitation, Quality of life, Self-efficacy, Symptom stability, Symptom frequency, Symptom burden, and Total symptoms (calculated as the mean of Symptom frequency and Symptom burden scores). Two summary scores were calculated: Clinical Summary (calculated as mean of Physical limitation and Total symptom scores) and Overall Summary (calculated as mean of Physical limitation, Social limitation, Total symptoms, and Quality of life scores). Domain and summary scores ranged from 0 (minimum) to 100 (maximum); higher scores represent better health status. Analysis done on ITT analysis set. Pre-specified intent of study was to compare results between tafamidis with placebo, irrespective of tafamidis doses. Here, 'n' = Subjects evaluable for this end point at specified categories.

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

End point timeframe:

Baseline, Month 30

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| End point values                     | Placebo             | Tafamidis            |  |  |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type                   | Reporting group     | Subject analysis set |  |  |
| Number of subjects analysed          | 177                 | 264                  |  |  |
| Units: units on a scale              |                     |                      |  |  |
| arithmetic mean (standard deviation) |                     |                      |  |  |
| Baseline (n=177, 264)                | 65.898 (± 21.7357)  | 67.274 (± 21.3561)   |  |  |
| Change at Month 30 (n=84,170)        | -14.637 (± 21.4078) | -3.855 (± 19.3075)   |  |  |

## Statistical analyses

|  |                                      |
|--|--------------------------------------|
| <b>Statistical analysis title</b>  | Tafamidis Vs. Placebo                |
| Statistical analysis description:<br>Change at Month 30: Overall Summary |                                      |
| Comparison groups  | Placebo v Tafamidis                  |
| Number of subjects included in analysis                                  | 441                                  |
| Analysis specification   | Pre-specified                        |
| Analysis type  | superiority                          |
| P-value  | < 0.0001                             |
| Method   | Mixed Model Repeated Measures ANCOVA |
| Parameter estimate   | LS Mean Difference                   |
| Point estimate   | 13.65                                |
| Confidence interval  |                                      |
| level  | 95 %                                 |
| sides  | 2-sided                              |
| lower limit  | 9.48                                 |
| upper limit  | 17.83                                |
| Variability estimate   | Standard error of the mean           |
| Dispersion value   | 2.13                                 |

## Secondary: Number of Subjects With Cardiovascular-Related Mortality

|   |   |
|---|---|
| End point title   | Number of Subjects With Cardiovascular-Related Mortality <sup>[7]</sup> |
| End point description:<br>Deaths adjudicated as CV-related and indeterminate are reported. Subjects who discontinued for transplantation (heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the same manner as death. The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation (post baseline hospitalization, study visit, or date of death). The pre-specified intent of this study was to compare the results between tafamidis with placebo, irrespective of the tafamidis doses. Therefore, this analysis was based on the pooled dose groups, as per the study protocol. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline up to Month 30   |   |

### Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| End point values            | Placebo         | Tafamidis            |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 177             | 264                  |  |  |
| Units: subjects             | 63              | 64                   |  |  |

## Statistical analyses

| Statistical analysis title   | Tafamidis Vs.Placebo           |
|--|--------------------------------|
| Statistical analysis description:  |                                |
| Hazard ratio from a Cox proportional hazards model with treatment, TTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) in the model. |                                |
| Comparison groups  | Placebo v Tafamidis            |
| Number of subjects included in analysis  | 441                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.0383                       |
| Method   | Cox proportional hazards model |
| Parameter estimate   | Hazard ratio (HR)              |
| Point estimate   | 0.691                          |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | 0.488                          |
| upper limit  | 0.98                           |

## Secondary: Percentage of Subjects With Stabilized Transthyretin (TTR) at Month 1

|   |  |
|---|--|
| End point title   | Percentage of Subjects With Stabilized Transthyretin (TTR) at Month 1 <sup>[8]</sup> |
| End point description:  |  |
| TTR stabilization is a measure of the degree of stabilization afforded the TTR molecule by tafamidis. The ITT analysis set included all subjects in the safety population (all randomized subjects who received at least 1 dose of double-blind medication) who had at least 1 post baseline efficacy evaluation (post baseline hospitalization, study visit, or date of death). The pre-specified intent of this study was to compare the results between tafamidis with placebo, irrespective of the tafamidis doses. Therefore, this analysis was based on the pooled dose groups, as per the study protocol. Here, 'Number analyzed' = Subjects evaluable for this end point. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Month 1   |  |

### Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All patients receiving active medication (Tafamidis 20mg and Tafamidis 80 mg) are included in the pooled analysis

| <b>End point values</b>       | Placebo         | Tafamidis            |  |  |
|-------------------------------|-----------------|----------------------|--|--|
| Subject group type            | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed   | 170             | 245                  |  |  |
| Units: percentage of subjects |                 |                      |  |  |
| number (not applicable)       | 3.5             | 86.1                 |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Tafamidis Vs.Placebo |
|---|----------------------|
| Comparison groups                       | Placebo v Tafamidis  |
| Number of subjects included in analysis | 415                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | < 0.0001             |
| Method                                  | Chi-squared          |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study drug (Month 31)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Analysis performed on safety population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Tafamidis 20 mg |
|-----------------------|-----------------|

Reporting group description:

Participants with variant transthyretin cardiomyopathy (TTR-CM) genotype or wild-type TTRCM genotype received one tafamidis 20 milligram (mg) capsule orally once daily for 30 months.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Tafamidis 80 mg |
|-----------------------|-----------------|

Reporting group description:

Participants with variant TTR-CM genotype or wild-type TTR-CM genotype received tafamidis 80 mg (4 capsules of 20 mg each) orally once daily for 30 months.

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

Reporting group description:

Participants with variant TTR-CM genotype or wild-type TTR-CM genotype received 4 placebo capsules matched to tafamidis orally once daily for 30 months.

| Serious adverse events  | Tafamidis 20 mg  | Tafamidis 80 mg    | Placebo            |
|---|------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events                   |                  |                    |                    |
| subjects affected / exposed   | 66 / 88 (75.00%) | 133 / 176 (75.57%) | 140 / 177 (79.10%) |
| number of deaths (all causes)                                       | 23               | 49                 | 72                 |
| number of deaths resulting from adverse events                      |                  |                    |                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                    |                    |
| Adenocarcinoma  |                  |                    |                    |
| subjects affected / exposed   | 1 / 88 (1.14%)   | 0 / 176 (0.00%)    | 0 / 177 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0              | 0 / 0              |
| Basal cell carcinoma  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 1 / 176 (0.57%)    | 0 / 177 (0.00%)    |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1              | 0 / 0              |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0              | 0 / 0              |
| Bladder cancer  |                  |                    |                    |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Bladder transitional cell carcinoma             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Breast cancer                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gallbladder adenocarcinoma                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Intraductal papilloma of breast                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Malignant melanoma                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Metastatic squamous cell carcinoma              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Oesophageal adenocarcinoma                      |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Rectal adenoma                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Renal neoplasm                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Testicular neoplasm                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Transitional cell carcinoma metastatic          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                |                 |                 |
| Aortic dissection                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Circulatory collapse                            |                |                 |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                                 |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Haematoma  |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypotension  |                |                 |                 |
| subjects affected / exposed                          | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Lymphoedema  |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                              |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Peripheral vascular disorder                         |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Shock haemorrhagic                                   |                |                 |                 |
| subjects affected / exposed                          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 1           |
| General disorders and administration site conditions |                |                 |                 |
| Asthenia   |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Chest discomfort                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Chest pain                                      |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Disease progression                             |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 4 / 176 (2.27%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 3          | 0 / 11          | 0 / 9           |
| General physical health deterioration           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Generalised oedema                              |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Incarcerated hernia                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Medical device site haematoma                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Oedema peripheral                               |                |                 |                 |

|   |                 |                   |                   |
|---|-----------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Peripheral swelling                             |                 |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)   | 2 / 177 (1.13%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Pyrexia   |                 |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 4 / 176 (2.27%)   | 0 / 177 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Sudden cardiac death                            |                 |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 1             |
| Sudden death                                    |                 |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |
| Death   |                 |                   |                   |
| subjects affected / exposed                     | 9 / 88 (10.23%) | 24 / 176 (13.64%) | 34 / 177 (19.21%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 24            | 0 / 34            |
| deaths causally related to treatment / all      | 0 / 9           | 0 / 24            | 0 / 34            |
| Immune system disorders                         |                 |                   |                   |
| Amyloidosis                                     |                 |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)  | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0             | 0 / 2             |
| Reproductive system and breast disorders        |                 |                   |                   |
| Benign prostatic hyperplasia                    |                 |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)  | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             | 0 / 0             |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Cervical dysplasia                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Spermatocele                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                |                 |                 |
| Acute pulmonary oedema                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Acute respiratory failure                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Asthma  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Choking   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cough   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Dyspnoea  |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 3 / 176 (1.70%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dyspnoea exertional                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Epistaxis                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haemoptysis                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haemothorax                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hiccups   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypoxia   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Interstitial lung disease                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lung disorder                                   |                |                 |                 |



|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pleural effusion                                |                |                 |                 |
| subjects affected / exposed                     | 5 / 88 (5.68%) | 6 / 176 (3.41%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 8           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonitis                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pulmonary mass                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pulmonary oedema                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pulmonary toxicity                              |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory acidosis                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory distress                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 1           |
| Psychiatric disorders                           |                |                 |                 |
| Completed suicide                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Confusional state                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Delirium  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Mental status changes                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Stress  |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Product issues                                  |                |                 |                 |
| Device connection issue                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Device dislocation                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Device malfunction                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Investigations                                  |                |                 |                 |
| Anticoagulation drug level above therapeutic    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Anticoagulation drug level below therapeutic    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Blood potassium decreased                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Blood sodium decreased                          |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Ejection fraction decreased                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| International normalised ratio increased        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Liver function test increased                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Streptococcus test positive                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Transaminases increased                         |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                 |                 |
| Concussion                                      |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Craniocerebral injury                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Facial bones fracture                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Fall  |                |                 |                 |
| subjects affected / exposed                     | 5 / 88 (5.68%) | 9 / 176 (5.11%) | 5 / 177 (2.82%) |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 11          | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Femoral neck fracture                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Forearm fracture                                |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Head injury                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Injury  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Joint injury                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Laceration                                      |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Limb injury                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lumbar vertebral fracture                       |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Muscle rupture                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Muscle strain                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Musculoskeletal foreign body                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Overdose  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Procedural hypotension                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Procedural pain                                 |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Skin abrasion                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Spinal compression fracture                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Tendon rupture                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tibia fracture                                  |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Vasoplegia syndrome                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Wound dehiscence                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                |                 |                 |
| Familial amyloidosis                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Cardiac disorders                               |                |                 |                 |
| Acute coronary syndrome                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Acute left ventricular failure                  |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |



|   |                |                  |                 |
|---|----------------|------------------|-----------------|
| Angina pectoris                                 |                |                  |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Angina unstable                                 |                |                  |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Aortic valve stenosis                           |                |                  |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Arrhythmia                                      |                |                  |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Arrhythmia supraventricular                     |                |                  |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Atrial fibrillation                             |                |                  |                 |
| subjects affected / exposed                     | 7 / 88 (7.95%) | 11 / 176 (6.25%) | 8 / 177 (4.52%) |
| occurrences causally related to treatment / all | 0 / 8          | 0 / 12           | 0 / 19          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Atrial flutter                                  |                |                  |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 4 / 176 (2.27%)  | 5 / 177 (2.82%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 5            | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Atrial tachycardia                              |                |                  |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0           |
| Atrial thrombosis                               |                |                  |                 |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Atrioventricular block                          |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Atrioventricular block complete                 |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 4 / 176 (2.27%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Atrioventricular block second degree            |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Bradycardia                                     |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 5 / 176 (2.84%)   | 5 / 177 (2.82%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Cardiac amyloidosis                             |                  |                   |                   |
| subjects affected / exposed                     | 2 / 88 (2.27%)   | 3 / 176 (1.70%)   | 5 / 177 (2.82%)   |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 4             | 0 / 3             |
| Cardiac arrest                                  |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 2 / 176 (1.14%)   | 6 / 177 (3.39%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2             | 0 / 6             |
| Cardiac failure                                 |                  |                   |                   |
| subjects affected / exposed                     | 16 / 88 (18.18%) | 34 / 176 (19.32%) | 39 / 177 (22.03%) |
| occurrences causally related to treatment / all | 0 / 25           | 0 / 50            | 0 / 61            |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 6             | 0 / 6             |
| Cardiac failure acute                           |                  |                   |                   |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 4 / 88 (4.55%)   | 23 / 176 (13.07%) | 17 / 177 (9.60%)  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 30            | 0 / 28            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 2             |
| Cardiac failure chronic                         |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 2 / 176 (1.14%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5             | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             | 0 / 0             |
| Cardiac failure congestive                      |                  |                   |                   |
| subjects affected / exposed                     | 15 / 88 (17.05%) | 20 / 176 (11.36%) | 32 / 177 (18.08%) |
| occurrences causally related to treatment / all | 0 / 17           | 0 / 31            | 0 / 46            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3             | 0 / 3             |
| Cardio-respiratory arrest                       |                  |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             | 0 / 0             |
| Cardiogenic shock                               |                  |                   |                   |
| subjects affected / exposed                     | 3 / 88 (3.41%)   | 2 / 176 (1.14%)   | 4 / 177 (2.26%)   |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             | 0 / 5             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 1             |
| Cardiomyopathy                                  |                  |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             | 0 / 0             |
| Cardiorenal syndrome                            |                  |                   |                   |
| subjects affected / exposed                     | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Chronic left ventricular failure                |                  |                   |                   |
| subjects affected / exposed                     | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Conduction disorder                             |                  |                   |                   |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Left ventricular failure                        |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 3 / 176 (1.70%) | 6 / 177 (3.39%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 4           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Myocardial depression                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Nodal rhythm                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pericardial effusion                            |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Right ventricular failure                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Sinus bradycardia                               |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Systolic dysfunction                            |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tachyarrhythmia                                 |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tachycardia                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ventricular arrhythmia                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ventricular extrasystoles                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ventricular fibrillation                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 1 / 1           |
| Ventricular tachycardia                         |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 88 (2.27%) | 2 / 176 (1.14%) | 7 / 177 (3.95%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                |                 |                 |
| Altered state of consciousness                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ataxia  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Carpal tunnel syndrome                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebral haemorrhage                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cervicobrachial syndrome                        |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dizziness                                       |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 5 / 177 (2.82%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           | 1 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dysarthria                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Embolic cerebral infarction                     |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Embolic stroke                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Epilepsy  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haemorrhage intracranial                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Hepatic encephalopathy                          |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lethargy  |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Memory impairment                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Metabolic encephalopathy                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Neuropathy peripheral                           |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Presyncope                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Seizure   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Somnolence                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Syncope   |                |                 |                 |



|   |                |                 |                  |
|---|----------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 6 / 176 (3.41%) | 10 / 177 (5.65%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 7           | 0 / 11           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Transient ischaemic attack                      |                |                 |                  |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Uraemic encephalopathy                          |                |                 |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Blood and lymphatic system disorders            |                |                 |                  |
| Anaemia   |                |                 |                  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Coagulopathy                                    |                |                 |                  |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Leukocytosis                                    |                |                 |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Microcytic anaemia                              |                |                 |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Neutrophilia                                    |                |                 |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0            |
| Eye disorders                                   |                |                 |                  |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| Cataract  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Conjunctival haemorrhage                        |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                |                 |                 |
| Abdominal pain                                  |                |                 |                 |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| Abdominal pain upper                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ascites   |                |                 |                 |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| Colitis   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Constipation                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Diverticulum                                    |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Duodenitis                                      |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastric haemorrhage                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastritis                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastritis haemorrhagic                          |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastroduodenal ulcer                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastrointestinal disorder                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haematemesis                                    |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haematochezia                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ileus   |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Impaired gastric emptying                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Melaena   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Obstructive pancreatitis                        |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Oesophagitis                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tongue disorder                                 |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Vomiting  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                |                 |                 |
| Cardiac cirrhosis                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cholecystitis                                   |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cholecystitis acute                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Ischaemic hepatitis                             |                |                 |                 |

|   |                 |                  |                  |
|---|-----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Skin and subcutaneous tissue disorders          |                 |                  |                  |
| Dermatitis contact                              |                 |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Erythema  |                 |                  |                  |
| subjects affected / exposed                     | 1 / 88 (1.14%)  | 0 / 176 (0.00%)  | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Neuropathic ulcer                               |                 |                  |                  |
| subjects affected / exposed                     | 1 / 88 (1.14%)  | 0 / 176 (0.00%)  | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Skin ulcer                                      |                 |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Stevens-Johnson syndrome                        |                 |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1            |
| Urticaria                                       |                 |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%)  | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0            |
| Renal and urinary disorders                     |                 |                  |                  |
| Acute kidney injury                             |                 |                  |                  |
| subjects affected / exposed                     | 9 / 88 (10.23%) | 13 / 176 (7.39%) | 15 / 177 (8.47%) |
| occurrences causally related to treatment / all | 1 / 10          | 0 / 14           | 0 / 22           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 1            |
| Azotaemia                                       |                 |                  |                  |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Calculus urinary                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| End stage renal disease                         |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haematuria                                      |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hydronephrosis                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Renal failure                                   |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| Renal impairment                                |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Renal injury                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urinary bladder haemorrhage                     |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urinary retention                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                 |                 |
| Arthralgia                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Arthritis                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Back pain                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gouty arthritis                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Haemarthrosis                                   |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Joint swelling                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Muscular weakness                               |                |                 |                 |



|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Neck pain                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Osteitis  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Spondylolisthesis                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Systemic lupus erythematosus                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                |                 |                 |
| Acute sinusitis                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Appendicitis                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Arthritis infective                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Bacteraemia                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Bacterial sepsis                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                |                 |                 |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Cystitis  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Endocarditis                                    |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Infected skin ulcer                             |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Infectious pleural effusion                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Influenza                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                |                 |                 |

|   |                |                  |                  |
|---|----------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Necrotising soft tissue infection               |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Ophthalmic herpes zoster                        |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Osteomyelitis                                   |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Parainfluenzae virus infection                  |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Pneumonia                                       |                |                  |                  |
| subjects affected / exposed                     | 6 / 88 (6.82%) | 13 / 176 (7.39%) | 12 / 177 (6.78%) |
| occurrences causally related to treatment / all | 0 / 6          | 0 / 14           | 0 / 13           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            | 0 / 1            |
| Pneumonia legionella                            |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 0            |
| Pneumonia pneumococcal                          |                |                  |                  |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 1            |
| Pyelonephritis                                  |                |                  |                  |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Rhinitis  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Sepsis  |                |                 |                 |
| subjects affected / exposed                     | 3 / 88 (3.41%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 2          | 0 / 0           | 0 / 1           |
| Septic arthritis staphylococcal                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Septic shock                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1           | 0 / 1           |
| Serratia infection                              |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Staphylococcal bacteraemia                      |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Staphylococcal infection                        |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0           |
| Staphylococcal sepsis                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Subcutaneous abscess                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tonsillitis                                     |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Tracheobronchitis                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 5 / 177 (2.82%) |
| occurrences causally related to treatment / all | 0 / 3          | 1 / 1           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Viral upper respiratory tract infection         |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                |                 |                 |
| Cachexia  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Dehydration                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 6 / 177 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Diabetes mellitus                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Electrolyte imbalance                           |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Failure to thrive                               |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Fluid overload                                  |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 2 / 176 (1.14%) | 6 / 177 (3.39%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2           | 0 / 12          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 1           |
| Fluid retention                                 |                |                 |                 |
| subjects affected / exposed                     | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Gout  |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypoalbuminaemia                                |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypokalaemia                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypomagnesaemia                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 4 / 177 (2.26%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Hypovolaemia                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 0 %



| <b>Non-serious adverse events</b>                                   | Tafamidis 20 mg  | Tafamidis 80 mg    | Placebo            |
|---|------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events               |                  |                    |                    |
| subjects affected / exposed   | 86 / 88 (97.73%) | 170 / 176 (96.59%) | 171 / 177 (96.61%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                    |                    |
| Acrochordon   |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 1 / 176 (0.57%)    | 0 / 177 (0.00%)    |
| occurrences (all)   | 0                | 1                  | 0                  |
| Basal cell carcinoma  |                  |                    |                    |
| subjects affected / exposed   | 4 / 88 (4.55%)   | 4 / 176 (2.27%)    | 4 / 177 (2.26%)    |
| occurrences (all)   | 5                | 9                  | 4                  |
| Bladder neoplasm  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 0 / 176 (0.00%)    | 1 / 177 (0.56%)    |
| occurrences (all)   | 0                | 0                  | 1                  |
| Cancer pain   |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 0 / 176 (0.00%)    | 1 / 177 (0.56%)    |
| occurrences (all)   | 0                | 0                  | 1                  |
| Haemangioma of skin   |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 1 / 176 (0.57%)    | 0 / 177 (0.00%)    |
| occurrences (all)   | 0                | 1                  | 0                  |
| Malignant melanoma  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 1 / 176 (0.57%)    | 0 / 177 (0.00%)    |
| occurrences (all)   | 0                | 1                  | 0                  |
| Melanocytic naevus  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 0 / 176 (0.00%)    | 1 / 177 (0.56%)    |
| occurrences (all)   | 0                | 0                  | 1                  |
| Metastatic squamous cell carcinoma                                  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 0 / 176 (0.00%)    | 1 / 177 (0.56%)    |
| occurrences (all)   | 0                | 0                  | 1                  |
| Neoplasm  |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 1 / 176 (0.57%)    | 0 / 177 (0.00%)    |
| occurrences (all)   | 0                | 1                  | 0                  |
| Neoplasm skin   |                  |                    |                    |
| subjects affected / exposed   | 0 / 88 (0.00%)   | 0 / 176 (0.00%)    | 1 / 177 (0.56%)    |
| occurrences (all)   | 0                | 0                  | 1                  |
| Neuroendocrine carcinoma of the skin                                |                  |                    |                    |

|   |                     |                      |                      |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                    | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Ocular neoplasm<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 88 (1.14%)<br>1 | 0 / 176 (0.00%)<br>0 | 0 / 177 (0.00%)<br>0 |
| Prostate cancer<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>3 | 1 / 177 (0.56%)<br>1 |
| Seborrhoeic keratosis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 88 (1.14%)<br>1 | 2 / 176 (1.14%)<br>2 | 0 / 177 (0.00%)<br>0 |
| Squamous cell carcinoma<br>subjects affected / exposed<br>occurrences (all)         | 0 / 88 (0.00%)<br>0 | 5 / 176 (2.84%)<br>6 | 2 / 177 (1.13%)<br>4 |
| Squamous cell carcinoma of skin<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 2 / 176 (1.14%)<br>2 | 2 / 177 (1.13%)<br>2 |
| Vascular disorders  |                     |                      |                      |
| Aortic aneurysm<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Aortic dilatation<br>subjects affected / exposed<br>occurrences (all)               | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Aortic stenosis<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 2 / 177 (1.13%)<br>3 |
| Arterial occlusive disease<br>subjects affected / exposed<br>occurrences (all)      | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Arteriosclerosis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 1 / 177 (0.56%)<br>1 |
| Bleeding varicose vein<br>subjects affected / exposed<br>occurrences (all)          | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1 | 1 / 177 (0.56%)<br>2 |

|                                       |                  |                   |                  |
|---------------------------------------|------------------|-------------------|------------------|
| Deep vein thrombosis                  |                  |                   |                  |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0                | 0                 | 1                |
| Embolism                              |                  |                   |                  |
| subjects affected / exposed           | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)  |
| occurrences (all)                     | 1                | 0                 | 0                |
| Haematoma                             |                  |                   |                  |
| subjects affected / exposed           | 2 / 88 (2.27%)   | 6 / 176 (3.41%)   | 8 / 177 (4.52%)  |
| occurrences (all)                     | 2                | 6                 | 9                |
| Haemorrhage                           |                  |                   |                  |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0                | 1                 | 1                |
| Hypertension                          |                  |                   |                  |
| subjects affected / exposed           | 1 / 88 (1.14%)   | 3 / 176 (1.70%)   | 4 / 177 (2.26%)  |
| occurrences (all)                     | 1                | 3                 | 4                |
| Hypotension                           |                  |                   |                  |
| subjects affected / exposed           | 11 / 88 (12.50%) | 19 / 176 (10.80%) | 17 / 177 (9.60%) |
| occurrences (all)                     | 12               | 22                | 18               |
| Jugular vein distension               |                  |                   |                  |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0                | 1                 | 1                |
| Lymphoedema                           |                  |                   |                  |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0                | 1                 | 1                |
| Orthostatic hypotension               |                  |                   |                  |
| subjects affected / exposed           | 2 / 88 (2.27%)   | 8 / 176 (4.55%)   | 5 / 177 (2.82%)  |
| occurrences (all)                     | 2                | 10                | 5                |
| Pallor                                |                  |                   |                  |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)  |
| occurrences (all)                     | 0                | 1                 | 0                |
| Peripheral arterial occlusive disease |                  |                   |                  |
| subjects affected / exposed           | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 1                | 1                 | 1                |
| Peripheral coldness                   |                  |                   |                  |
| subjects affected / exposed           | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)  |
| occurrences (all)                     | 1                | 0                 | 1                |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| Peripheral vascular disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0    | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>2   |
| Peripheral venous disease<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0    | 1 / 176 (0.57%)<br>1   | 1 / 177 (0.56%)<br>1   |
| Raynaud's phenomenon<br>subjects affected / exposed<br>occurrences (all)         | 0 / 88 (0.00%)<br>0    | 0 / 176 (0.00%)<br>0   | 2 / 177 (1.13%)<br>2   |
| Subclavian vein thrombosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0    | 1 / 176 (0.57%)<br>1   | 0 / 177 (0.00%)<br>0   |
| Thrombosis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 88 (0.00%)<br>0    | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Varicophlebitis<br>subjects affected / exposed<br>occurrences (all)              | 0 / 88 (0.00%)<br>0    | 1 / 176 (0.57%)<br>1   | 0 / 177 (0.00%)<br>0   |
| Varicose vein<br>subjects affected / exposed<br>occurrences (all)                | 2 / 88 (2.27%)<br>2    | 1 / 176 (0.57%)<br>1   | 1 / 177 (0.56%)<br>1   |
| General disorders and administration<br>site conditions                          |                        |                        |                        |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                     | 11 / 88 (12.50%)<br>16 | 16 / 176 (9.09%)<br>20 | 11 / 177 (6.21%)<br>17 |
| Atrophy<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 88 (0.00%)<br>0    | 2 / 176 (1.14%)<br>2   | 0 / 177 (0.00%)<br>0   |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)             | 3 / 88 (3.41%)<br>3    | 8 / 176 (4.55%)<br>8   | 8 / 177 (4.52%)<br>9   |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 88 (3.41%)<br>3    | 7 / 176 (3.98%)<br>7   | 8 / 177 (4.52%)<br>9   |
| Chills   |                        |                        |                        |

|                              |                  |                   |                   |
|------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed  | 2 / 88 (2.27%)   | 2 / 176 (1.14%)   | 2 / 177 (1.13%)   |
| occurrences (all)            | 2                | 3                 | 2                 |
| Condition aggravated         |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 1                 | 1                 |
| Cyst rupture                 |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)            | 0                | 1                 | 0                 |
| Decreased activity           |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 0                 | 1                 |
| Discomfort                   |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 0                 | 1                 |
| Disease progression          |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 0                 | 2                 |
| Early satiety                |                  |                   |                   |
| subjects affected / exposed  | 2 / 88 (2.27%)   | 2 / 176 (1.14%)   | 3 / 177 (1.69%)   |
| occurrences (all)            | 2                | 2                 | 3                 |
| Effusion                     |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 0                 | 1                 |
| Exercise tolerance decreased |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 4 / 177 (2.26%)   |
| occurrences (all)            | 0                | 1                 | 10                |
| Facial pain                  |                  |                   |                   |
| subjects affected / exposed  | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)            | 2                | 0                 | 0                 |
| Fatigue                      |                  |                   |                   |
| subjects affected / exposed  | 16 / 88 (18.18%) | 29 / 176 (16.48%) | 33 / 177 (18.64%) |
| occurrences (all)            | 23               | 33                | 48                |
| Feeling abnormal             |                  |                   |                   |
| subjects affected / exposed  | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)            | 0                | 1                 | 1                 |
| Feeling cold                 |                  |                   |                   |

|                                       |                |                 |                  |
|---------------------------------------|----------------|-----------------|------------------|
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 1               | 1                |
| Gait disturbance                      |                |                 |                  |
| subjects affected / exposed           | 4 / 88 (4.55%) | 4 / 176 (2.27%) | 11 / 177 (6.21%) |
| occurrences (all)                     | 4              | 4               | 11               |
| General physical health deterioration |                |                 |                  |
| subjects affected / exposed           | 1 / 88 (1.14%) | 4 / 176 (2.27%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 4              | 4               | 1                |
| Generalised oedema                    |                |                 |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0               | 1                |
| Ill-defined disorder                  |                |                 |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)                     | 0              | 1               | 0                |
| Impaired healing                      |                |                 |                  |
| subjects affected / exposed           | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%)  |
| occurrences (all)                     | 1              | 1               | 2                |
| Implant site haematoma                |                |                 |                  |
| subjects affected / exposed           | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 2              | 0               | 1                |
| Implant site pain                     |                |                 |                  |
| subjects affected / exposed           | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 2              | 1               | 1                |
| Inflammation                          |                |                 |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 4               | 1                |
| Influenza like illness                |                |                 |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 1               | 1                |
| Malaise                               |                |                 |                  |
| subjects affected / exposed           | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 4 / 177 (2.26%)  |
| occurrences (all)                     | 1              | 2               | 5                |
| Mass                                  |                |                 |                  |
| subjects affected / exposed           | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)                     | 1              | 0               | 0                |
| Multiple organ dysfunction syndrome   |                |                 |                  |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed             | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| Non-cardiac chest pain                  |                  |                   |                   |
| subjects affected / exposed             | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                       | 1                | 1                 | 0                 |
| Oedema                                  |                  |                   |                   |
| subjects affected / exposed             | 7 / 88 (7.95%)   | 11 / 176 (6.25%)  | 20 / 177 (11.30%) |
| occurrences (all)                       | 7                | 22                | 22                |
| Oedema peripheral                       |                  |                   |                   |
| subjects affected / exposed             | 17 / 88 (19.32%) | 29 / 176 (16.48%) | 31 / 177 (17.51%) |
| occurrences (all)                       | 19               | 42                | 42                |
| Pain                                    |                  |                   |                   |
| subjects affected / exposed             | 1 / 88 (1.14%)   | 6 / 176 (3.41%)   | 2 / 177 (1.13%)   |
| occurrences (all)                       | 1                | 6                 | 2                 |
| Peripheral swelling                     |                  |                   |                   |
| subjects affected / exposed             | 2 / 88 (2.27%)   | 6 / 176 (3.41%)   | 7 / 177 (3.95%)   |
| occurrences (all)                       | 3                | 7                 | 7                 |
| Pseudocyst                              |                  |                   |                   |
| subjects affected / exposed             | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                       | 0                | 0                 | 1                 |
| Pyrexia                                 |                  |                   |                   |
| subjects affected / exposed             | 1 / 88 (1.14%)   | 3 / 176 (1.70%)   | 4 / 177 (2.26%)   |
| occurrences (all)                       | 2                | 3                 | 4                 |
| Systemic inflammatory response syndrome |                  |                   |                   |
| subjects affected / exposed             | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| Temperature intolerance                 |                  |                   |                   |
| subjects affected / exposed             | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                       | 1                | 1                 | 0                 |
| Haemorrhagic cyst                       |                  |                   |                   |
| subjects affected / exposed             | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| Immune system disorders                 |                  |                   |                   |
| Dust allergy                            |                  |                   |                   |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed              | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0               |
| Hypersensitivity                         |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0               |
| Seasonal allergy                         |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)                        | 0              | 2               | 0               |
| Type IV hypersensitivity reaction        |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                        | 0              | 0               | 1               |
| Social circumstances                     |                |                 |                 |
| Immobile                                 |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                        | 0              | 0               | 1               |
| Reproductive system and breast disorders |                |                 |                 |
| Benign prostatic hyperplasia             |                |                 |                 |
| subjects affected / exposed              | 2 / 88 (2.27%) | 6 / 176 (3.41%) | 7 / 177 (3.95%) |
| occurrences (all)                        | 2              | 7               | 7               |
| Breast engorgement                       |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                        | 0              | 0               | 1               |
| Breast enlargement                       |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                        | 0              | 1               | 1               |
| Breast mass                              |                |                 |                 |
| subjects affected / exposed              | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                        | 1              | 1               | 1               |
| Breast pain                              |                |                 |                 |
| subjects affected / exposed              | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                        | 1              | 0               | 0               |
| Breast swelling                          |                |                 |                 |
| subjects affected / exposed              | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                        | 0              | 1               | 0               |
| Breast tenderness                        |                |                 |                 |



|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 88 (1.14%) | 5 / 176 (2.84%) | 3 / 177 (1.69%) |
| occurrences (all)                               | 1              | 5               | 3               |
| Cervix disorder                                 |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0               |
| Erectile dysfunction                            |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences (all)                               | 0              | 2               | 3               |
| Genital rash                                    |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0               |
| Gynaecomastia                                   |                |                 |                 |
| subjects affected / exposed                     | 4 / 88 (4.55%) | 9 / 176 (5.11%) | 6 / 177 (3.39%) |
| occurrences (all)                               | 4              | 9               | 6               |
| Nipple pain                                     |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences (all)                               | 1              | 1               | 3               |
| Oedema genital                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                               | 0              | 0               | 1               |
| Pelvic pain                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0               |
| Penile haemorrhage                              |                |                 |                 |
| subjects affected / exposed                     | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0               |
| Prostatomegaly                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0               |
| Scrotal oedema                                  |                |                 |                 |
| subjects affected / exposed                     | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0               |
| Respiratory, thoracic and mediastinal disorders |                |                 |                 |
| Acute respiratory failure                       |                |                 |                 |

|                                       |                  |                   |                   |
|---------------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed           | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                     | 1                | 1                 | 0                 |
| Apnoea                                |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                     | 0                | 0                 | 1                 |
| Asthma                                |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                     | 0                | 1                 | 0                 |
| Atelectasis                           |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 3 / 176 (1.70%)   | 3 / 177 (1.69%)   |
| occurrences (all)                     | 0                | 3                 | 3                 |
| Bronchial disorder                    |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 2 / 176 (1.14%)   | 0 / 177 (0.00%)   |
| occurrences (all)                     | 0                | 2                 | 0                 |
| Bronchial hyperreactivity             |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                     | 0                | 0                 | 1                 |
| Bronchitis chronic                    |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                     | 0                | 0                 | 1                 |
| Bronchospasm                          |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                     | 0                | 1                 | 0                 |
| Cheyne-Stokes respiration             |                  |                   |                   |
| subjects affected / exposed           | 0 / 88 (0.00%)   | 2 / 176 (1.14%)   | 1 / 177 (0.56%)   |
| occurrences (all)                     | 0                | 2                 | 1                 |
| Chronic obstructive pulmonary disease |                  |                   |                   |
| subjects affected / exposed           | 2 / 88 (2.27%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)                     | 2                | 1                 | 1                 |
| Cough                                 |                  |                   |                   |
| subjects affected / exposed           | 16 / 88 (18.18%) | 20 / 176 (11.36%) | 30 / 177 (16.95%) |
| occurrences (all)                     | 23               | 27                | 35                |
| Dyspnoea                              |                  |                   |                   |
| subjects affected / exposed           | 21 / 88 (23.86%) | 27 / 176 (15.34%) | 51 / 177 (28.81%) |
| occurrences (all)                     | 26               | 38                | 69                |

|                                    |                |                  |                  |
|------------------------------------|----------------|------------------|------------------|
| Dyspnoea at rest                   |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                  | 0              | 0                | 1                |
| Dyspnoea exertional                |                |                  |                  |
| subjects affected / exposed        | 5 / 88 (5.68%) | 10 / 176 (5.68%) | 13 / 177 (7.34%) |
| occurrences (all)                  | 5              | 11               | 16               |
| Dyspnoea paroxysmal nocturnal      |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 3 / 176 (1.70%)  | 5 / 177 (2.82%)  |
| occurrences (all)                  | 0              | 4                | 7                |
| Emphysema                          |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences (all)                  | 0              | 1                | 1                |
| Epistaxis                          |                |                  |                  |
| subjects affected / exposed        | 2 / 88 (2.27%) | 12 / 176 (6.82%) | 14 / 177 (7.91%) |
| occurrences (all)                  | 3              | 12               | 22               |
| Haemoptysis                        |                |                  |                  |
| subjects affected / exposed        | 2 / 88 (2.27%) | 3 / 176 (1.70%)  | 3 / 177 (1.69%)  |
| occurrences (all)                  | 2              | 3                | 3                |
| Hyperventilation                   |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                  | 0              | 0                | 1                |
| Hypoxia                            |                |                  |                  |
| subjects affected / exposed        | 1 / 88 (1.14%) | 2 / 176 (1.14%)  | 3 / 177 (1.69%)  |
| occurrences (all)                  | 1              | 2                | 3                |
| Laryngeal disorder                 |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                  | 0              | 1                | 0                |
| Increased upper airway secretion   |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                  | 0              | 1                | 0                |
| Laryngeal erythema                 |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                  | 0              | 0                | 1                |
| Lower respiratory tract congestion |                |                  |                  |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                  | 0              | 1                | 0                |

|                              |                |                  |                   |
|------------------------------|----------------|------------------|-------------------|
| Lung disorder                |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 3 / 176 (1.70%)  | 0 / 177 (0.00%)   |
| occurrences (all)            | 0              | 4                | 0                 |
| Lung infiltration            |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)            | 0              | 1                | 0                 |
| Nasal congestion             |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 3 / 177 (1.69%)   |
| occurrences (all)            | 0              | 1                | 3                 |
| Nasal dryness                |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)            | 0              | 0                | 1                 |
| Nasal inflammation           |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)            | 0              | 1                | 0                 |
| Nasal mucosal disorder       |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)            | 0              | 1                | 0                 |
| Obstructive airways disorder |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)            | 0              | 0                | 1                 |
| Oropharyngeal discomfort     |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)            | 0              | 0                | 1                 |
| Oropharyngeal pain           |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 4 / 176 (2.27%)  | 4 / 177 (2.26%)   |
| occurrences (all)            | 0              | 4                | 4                 |
| Orthopnoea                   |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 5 / 176 (2.84%)  | 4 / 177 (2.26%)   |
| occurrences (all)            | 0              | 7                | 4                 |
| Painful respiration          |                |                  |                   |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)            | 0              | 1                | 1                 |
| Pleural effusion             |                |                  |                   |
| subjects affected / exposed  | 8 / 88 (9.09%) | 12 / 176 (6.82%) | 31 / 177 (17.51%) |
| occurrences (all)            | 11             | 16               | 42                |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Pleuritic pain              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Pneumomediastinum           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Pneumothorax                |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)           | 1              | 2               | 2               |
| Productive cough            |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 7 / 176 (3.98%) | 2 / 177 (1.13%) |
| occurrences (all)           | 2              | 7               | 2               |
| Pulmonary congestion        |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 1               | 2               |
| Pulmonary embolism          |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 1               | 0               |
| Pulmonary hypertension      |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 2               | 2               |
| Pulmonary mass              |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 3 / 176 (1.70%) | 0 / 177 (0.00%) |
| occurrences (all)           | 2              | 3               | 0               |
| Pulmonary oedema            |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 4 / 177 (2.26%) |
| occurrences (all)           | 1              | 0               | 4               |
| Rales                       |                |                 |                 |
| subjects affected / exposed | 3 / 88 (3.41%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences (all)           | 3              | 2               | 3               |
| Reflux laryngitis           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Respiratory disorder        |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 0               | 1               |

|                                    |                |                 |                 |
|------------------------------------|----------------|-----------------|-----------------|
| Respiratory distress               |                |                 |                 |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0               |
| Respiratory failure                |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 3 / 177 (1.69%) |
| occurrences (all)                  | 0              | 0               | 3               |
| Respiratory tract congestion       |                |                 |                 |
| subjects affected / exposed        | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)                  | 2              | 2               | 2               |
| Rhinitis allergic                  |                |                 |                 |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                  | 1              | 0               | 2               |
| Rhinorrhoea                        |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 4 / 177 (2.26%) |
| occurrences (all)                  | 0              | 1               | 4               |
| Rhonchi                            |                |                 |                 |
| subjects affected / exposed        | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0               |
| Sinus congestion                   |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                  | 0              | 0               | 2               |
| Sleep apnoea syndrome              |                |                 |                 |
| subjects affected / exposed        | 2 / 88 (2.27%) | 8 / 176 (4.55%) | 6 / 177 (3.39%) |
| occurrences (all)                  | 2              | 9               | 10              |
| Sneezing                           |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                  | 0              | 0               | 1               |
| Sputum retention                   |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                  | 0              | 0               | 2               |
| Upper respiratory tract congestion |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                  | 0              | 0               | 1               |
| Upper-airway cough syndrome        |                |                 |                 |
| subjects affected / exposed        | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0               |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| Vasomotor rhinitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 88 (1.14%)<br>2 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Vocal cord dysfunction<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 88 (1.14%)<br>2 | 1 / 176 (0.57%)<br>1 | 2 / 177 (1.13%)<br>3 |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 88 (2.27%)<br>2 | 1 / 176 (0.57%)<br>1 | 2 / 177 (1.13%)<br>2 |
| Psychiatric disorders  |                     |                      |                      |
| Acrophobia<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Adjustment disorder<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 2 / 177 (1.13%)<br>2 |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 88 (1.14%)<br>1 | 8 / 176 (4.55%)<br>8 | 5 / 177 (2.82%)<br>6 |
| Cardiovascular somatic symptom<br>disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 88 (1.14%)<br>2 | 3 / 176 (1.70%)<br>3 | 4 / 177 (2.26%)<br>4 |
| Delirium<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 88 (1.14%)<br>1 | 3 / 176 (1.70%)<br>3 | 3 / 177 (1.69%)<br>3 |
| Depressed mood   |                     |                      |                      |

|                             |                  |                   |                   |
|-----------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 3 / 177 (1.69%)   |
| occurrences (all)           | 0                | 0                 | 3                 |
| Depression                  |                  |                   |                   |
| subjects affected / exposed | 6 / 88 (6.82%)   | 7 / 176 (3.98%)   | 8 / 177 (4.52%)   |
| occurrences (all)           | 6                | 7                 | 10                |
| Disorientation              |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Dysphemia                   |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Hallucination               |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 1                | 1                 | 1                 |
| Insomnia                    |                  |                   |                   |
| subjects affected / exposed | 12 / 88 (13.64%) | 20 / 176 (11.36%) | 22 / 177 (12.43%) |
| occurrences (all)           | 13               | 23                | 27                |
| Major depression            |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 2                 |
| Mental status changes       |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Nervousness                 |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Nightmare                   |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 1                 | 1                 |
| Organic brain syndrome      |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Panic attack                |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 0                 | 0                 |
| Persecutory delusion        |                  |                   |                   |



|   |                     |                      |                      |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Stress<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>2 |
| Product issues<br>Device computer issue<br>subjects affected / exposed<br>occurrences (all)       | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Device dislocation<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 2 / 177 (1.13%)<br>2 |
| Device inappropriate shock delivery<br>subjects affected / exposed<br>occurrences (all)           | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>1 |
| Device loosening<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 88 (1.14%)<br>1 | 0 / 176 (0.00%)<br>0 | 0 / 177 (0.00%)<br>0 |
| Device malfunction<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>2 | 0 / 177 (0.00%)<br>0 |
| Device stimulation issue<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 2 / 177 (1.13%)<br>3 |
| Hepatobiliary disorders<br>Bile duct stenosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Cholecystitis   |                     |                      |                      |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1               | 1               |
| Cholelithiasis              |                |                 |                 |
| subjects affected / exposed | 4 / 88 (4.55%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 4              | 0               | 2               |
| Cholestasis                 |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 2               | 1               |
| Hepatic cirrhosis           |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Hepatic cyst                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Hepatic congestion          |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 2 / 177 (1.13%) |
| occurrences (all)           | 2              | 4               | 2               |
| Hepatic pain                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Hepatic steatosis           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 0               | 2               |
| Hepatitis acute             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Hepatomegaly                |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 3               | 1               |
| Ischaemic hepatitis         |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Jaundice                    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Jaundice cholestatic        |                |                 |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 0              | 1               | 1               |
| Portal vein thrombosis                       |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Hyperbilirubinaemia                          |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)                            | 1              | 2               | 3               |
| Investigations                               |                |                 |                 |
| Alanine aminotransferase increased           |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 0              | 0               | 1               |
| Anticoagulation drug level above therapeutic |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 4 / 177 (2.26%) |
| occurrences (all)                            | 0              | 1               | 4               |
| Anticoagulation drug level below therapeutic |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 1              | 1               | 0               |
| Arterial bruit                               |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Aspartate aminotransferase increased         |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 0              | 3               | 1               |
| Bence Jones protein urine present            |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 0              | 0               | 1               |
| Blood albumin decreased                      |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 1              | 0               | 1               |
| Blood alkaline phosphatase increased         |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)                            | 0              | 1               | 2               |
| Blood bicarbonate decreased                  |                |                 |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 0               | 1               |
| Blood bilirubin increased              |                |                 |                 |
| subjects affected / exposed            | 4 / 88 (4.55%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 4              | 4               | 1               |
| Blood chloride decreased               |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                      | 0              | 1               | 0               |
| Blood creatine increased               |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                      | 0              | 1               | 0               |
| Blood creatine phosphokinase increased |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 1               | 1               |
| Blood creatinine abnormal              |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 0               | 1               |
| Blood creatinine increased             |                |                 |                 |
| subjects affected / exposed            | 3 / 88 (3.41%) | 9 / 176 (5.11%) | 8 / 177 (4.52%) |
| occurrences (all)                      | 4              | 9               | 8               |
| Blood glucose increased                |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 2               | 1               |
| Blood lactate dehydrogenase increased  |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 0               | 1               |
| Blood lactic acid increased            |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                      | 0              | 0               | 1               |
| Blood potassium abnormal               |                |                 |                 |
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                      | 0              | 0               | 2               |
| Blood potassium decreased              |                |                 |                 |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                 | 1 / 88 (1.14%) | 4 / 176 (2.27%) | 5 / 177 (2.82%) |
| occurrences (all)                           | 1              | 4               | 5               |
| Blood potassium increased                   |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 4 / 177 (2.26%) |
| occurrences (all)                           | 0              | 0               | 4               |
| Blood pressure decreased                    |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                           | 0              | 0               | 2               |
| Blood pressure increased                    |                |                 |                 |
| subjects affected / exposed                 | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                           | 1              | 0               | 0               |
| Blood pressure systolic decreased           |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                           | 0              | 1               | 0               |
| Blood sodium decreased                      |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                           | 0              | 0               | 1               |
| Blood thyroid stimulating hormone decreased |                |                 |                 |
| subjects affected / exposed                 | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                           | 1              | 0               | 0               |
| Blood thyroid stimulating hormone increased |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 5 / 177 (2.82%) |
| occurrences (all)                           | 0              | 1               | 5               |
| Blood urea increased                        |                |                 |                 |
| subjects affected / exposed                 | 3 / 88 (3.41%) | 8 / 176 (4.55%) | 5 / 177 (2.82%) |
| occurrences (all)                           | 3              | 8               | 5               |
| Blood uric acid increased                   |                |                 |                 |
| subjects affected / exposed                 | 3 / 88 (3.41%) | 8 / 176 (4.55%) | 5 / 177 (2.82%) |
| occurrences (all)                           | 3              | 8               | 5               |
| Blood urine present                         |                |                 |                 |
| subjects affected / exposed                 | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)                           | 0              | 2               | 0               |
| Body temperature decreased                  |                |                 |                 |

|                                      |                |                 |                  |
|--------------------------------------|----------------|-----------------|------------------|
| subjects affected / exposed          | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 2               | 0                |
| Breath sounds abnormal               |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%)  |
| occurrences (all)                    | 0              | 1               | 3                |
| C-reactive protein increased         |                |                 |                  |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)                    | 1              | 0               | 0                |
| Cardiac murmur                       |                |                 |                  |
| subjects affected / exposed          | 2 / 88 (2.27%) | 3 / 176 (1.70%) | 4 / 177 (2.26%)  |
| occurrences (all)                    | 2              | 3               | 4                |
| Crystal urine present                |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0                |
| Drug level above therapeutic         |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0                |
| Ejection fraction decreased          |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 5 / 177 (2.82%)  |
| occurrences (all)                    | 0              | 2               | 5                |
| Electrocardiogram QT prolonged       |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 1               | 1                |
| Electrocardiogram abnormal           |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 0               | 1                |
| Gamma-glutamyltransferase increased  |                |                 |                  |
| subjects affected / exposed          | 3 / 88 (3.41%) | 9 / 176 (5.11%) | 11 / 177 (6.21%) |
| occurrences (all)                    | 3              | 9               | 11               |
| Glomerular filtration rate decreased |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 1               | 0                |
| Haemoglobin decreased                |                |                 |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 1               | 1                |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| Heart rate decreased   |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)  | 0              | 1               | 0               |
| Heart rate increased   |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)  | 0              | 0               | 2               |
| Heart rate irregular   |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)  | 0              | 1               | 1               |
| Hepatic enzyme increased                                     |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)  | 0              | 0               | 1               |
| Human epidermal growth factor<br>receptor decreased          |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)  | 0              | 0               | 1               |
| Human rhinovirus test positive                               |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)  | 0              | 1               | 0               |
| Inflammatory marker increased                                |                |                 |                 |
| subjects affected / exposed                                  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)  | 1              | 0               | 0               |
| International normalised ratio<br>decreased                  |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)  | 0              | 0               | 1               |
| International normalised ratio<br>increased                  |                |                 |                 |
| subjects affected / exposed                                  | 5 / 88 (5.68%) | 4 / 176 (2.27%) | 4 / 177 (2.26%) |
| occurrences (all)  | 6              | 4               | 4               |
| Liver function test abnormal                                 |                |                 |                 |
| subjects affected / exposed                                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)  | 0              | 0               | 2               |
| Liver function test increased                                |                |                 |                 |
| subjects affected / exposed                                  | 2 / 88 (2.27%) | 5 / 176 (2.84%) | 2 / 177 (1.13%) |
| occurrences (all)  | 2              | 5               | 2               |
| N-terminal prohormone brain<br>natriuretic peptide increased |                |                 |                 |

|                                      |                |                 |                 |
|--------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 0              | 2               | 1               |
| Occult blood positive                |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                    | 0              | 0               | 2               |
| Optic nerve cup/disc ratio increased |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 1              | 0               | 0               |
| Oxygen saturation abnormal           |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences (all)                    | 0              | 2               | 2               |
| Oxygen saturation decreased          |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 0              | 1               | 2               |
| Platelet count decreased             |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)                    | 1              | 1               | 2               |
| Prostatic specific antigen increased |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                    | 0              | 0               | 2               |
| Protein urine present                |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0               |
| Prothrombin time prolonged           |                |                 |                 |
| subjects affected / exposed          | 3 / 88 (3.41%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 3              | 3               | 1               |
| Pulmonary function test decreased    |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 0              | 0               | 1               |
| Pulse absent                         |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0               |
| Red blood cell count decreased       |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0               |
| Thyroid function test abnormal       |                |                 |                 |



|                                   |                |                  |                   |
|-----------------------------------|----------------|------------------|-------------------|
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 0                | 1                 |
| Thyroxine decreased               |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 1                | 1                 |
| Transaminases increased           |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 3 / 177 (1.69%)   |
| occurrences (all)                 | 0              | 2                | 4                 |
| Troponin increased                |                |                  |                   |
| subjects affected / exposed       | 1 / 88 (1.14%) | 2 / 176 (1.14%)  | 4 / 177 (2.26%)   |
| occurrences (all)                 | 1              | 2                | 4                 |
| Urobilinogen urine increased      |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 1                | 0                 |
| Venous pressure jugular abnormal  |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 0                | 1                 |
| Venous pressure jugular increased |                |                  |                   |
| subjects affected / exposed       | 4 / 88 (4.55%) | 4 / 176 (2.27%)  | 9 / 177 (5.08%)   |
| occurrences (all)                 | 5              | 4                | 12                |
| Vitamin D decreased               |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 2 / 177 (1.13%)   |
| occurrences (all)                 | 0              | 2                | 2                 |
| Waist circumference increased     |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 2                | 0                 |
| Weight decreased                  |                |                  |                   |
| subjects affected / exposed       | 6 / 88 (6.82%) | 8 / 176 (4.55%)  | 18 / 177 (10.17%) |
| occurrences (all)                 | 6              | 8                | 19                |
| Weight increased                  |                |                  |                   |
| subjects affected / exposed       | 7 / 88 (7.95%) | 13 / 176 (7.39%) | 12 / 177 (6.78%)  |
| occurrences (all)                 | 8              | 20               | 12                |
| White blood cell count decreased  |                |                  |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 1                | 1                 |
| Injury, poisoning and procedural  |                |                  |                   |

|                             |                |                  |                 |
|-----------------------------|----------------|------------------|-----------------|
| complications               |                |                  |                 |
| Abdominal injury            |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0                | 1               |
| Animal bite                 |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0                | 1               |
| Arthropod bite              |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1                | 1               |
| Arthropod sting             |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1                | 0               |
| Back injury                 |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0                | 1               |
| Bone fissure                |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1                | 0               |
| Bursa injury                |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0                | 2               |
| Cervical vertebral fracture |                |                  |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 0                | 1               |
| Chest injury                |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1                | 1               |
| Compression fracture        |                |                  |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0                | 1               |
| Contusion                   |                |                  |                 |
| subjects affected / exposed | 6 / 88 (6.82%) | 11 / 176 (6.25%) | 5 / 177 (2.82%) |
| occurrences (all)           | 6              | 14               | 6               |
| Craniocerebral injury       |                |                  |                 |

|                             |                  |                   |                   |
|-----------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 1                | 0                 | 2                 |
| Electric shock              |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Excoriation                 |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Eye contusion               |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 1                 | 1                 |
| Face injury                 |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Facial bones fracture       |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 1                 | 0                 |
| Fall                        |                  |                   |                   |
| subjects affected / exposed | 24 / 88 (27.27%) | 38 / 176 (21.59%) | 40 / 177 (22.60%) |
| occurrences (all)           | 36               | 50                | 69                |
| Femoral neck fracture       |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Femur fracture              |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 0                 | 0                 |
| Foot fracture               |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 1                 | 1                 |
| Hand fracture               |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences (all)           | 0                | 1                 | 2                 |
| Head injury                 |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 5 / 176 (2.84%)   | 2 / 177 (1.13%)   |
| occurrences (all)           | 1                | 5                 | 2                 |
| Hip fracture                |                  |                   |                   |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 0               | 1               |
| Incision site erythema      |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Incision site pain          |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 2               | 1               |
| Injury                      |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 1               | 0               |
| Joint injury                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 3               | 1               |
| Laceration                  |                |                 |                 |
| subjects affected / exposed | 3 / 88 (3.41%) | 6 / 176 (3.41%) | 3 / 177 (1.69%) |
| occurrences (all)           | 3              | 6               | 3               |
| Ligament injury             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Ligament sprain             |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)           | 2              | 1               | 2               |
| Limb injury                 |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 1 / 176 (0.57%) | 4 / 177 (2.26%) |
| occurrences (all)           | 2              | 1               | 4               |
| Lip injury                  |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Lower limb fracture         |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Lumbar vertebral fracture   |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Meniscus injury             |                |                 |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 1               | 0               |
| Metal poisoning             |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Muscle injury               |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 0               | 1               |
| Muscle rupture              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Muscle strain               |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 0               | 2               |
| Overdose                    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1               | 1               |
| Pelvic fracture             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Periorbital haemorrhage     |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Post procedural haematoma   |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Post procedural haemorrhage |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 1               | 2               |
| Post procedural swelling    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Procedural pain             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 2               | 4               |
| Rib fracture                |                |                 |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 88 (2.27%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences (all)           | 2              | 2               | 4               |
| Scar                        |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 2               | 0               |
| Seroma                      |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Skeletal injury             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Skin abrasion               |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 5 / 176 (2.84%) | 5 / 177 (2.82%) |
| occurrences (all)           | 1              | 5               | 5               |
| Skin injury                 |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Spinal column injury        |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Spinal compression fracture |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 1              | 0               | 2               |
| Subcutaneous haematoma      |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Subdural haematoma          |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 3               | 0               |
| Sunburn                     |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Suture related complication |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Thermal burn                |                |                 |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed                | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 1               | 2               |
| Thoracic vertebral fracture                |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                          | 0              | 1               | 0               |
| Tooth fracture                             |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 0               | 1               |
| Upper limb fracture                        |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 0               | 1               |
| Wound                                      |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 4               | 1               |
| Wrist fracture                             |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 0               | 1               |
| Skin wound                                 |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                          | 0              | 1               | 0               |
| Congenital, familial and genetic disorders |                |                 |                 |
| Dermoid cyst                               |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                          | 0              | 1               | 0               |
| Hydrocele                                  |                |                 |                 |
| subjects affected / exposed                | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                          | 1              | 0               | 0               |
| Phimosis                                   |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 0               | 1               |
| Cardiac disorders                          |                |                 |                 |
| Accelerated idioventricular rhythm         |                |                 |                 |
| subjects affected / exposed                | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                          | 0              | 0               | 1               |
| Acute myocardial infarction                |                |                 |                 |

|                                  |                  |                   |                   |
|----------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed      | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)                | 0                | 1                 | 1                 |
| Angina pectoris                  |                  |                   |                   |
| subjects affected / exposed      | 2 / 88 (2.27%)   | 3 / 176 (1.70%)   | 1 / 177 (0.56%)   |
| occurrences (all)                | 2                | 3                 | 1                 |
| Aortic valve incompetence        |                  |                   |                   |
| subjects affected / exposed      | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences (all)                | 0                | 1                 | 2                 |
| Aortic valve stenosis            |                  |                   |                   |
| subjects affected / exposed      | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 2 / 177 (1.13%)   |
| occurrences (all)                | 0                | 0                 | 2                 |
| Arrhythmia                       |                  |                   |                   |
| subjects affected / exposed      | 0 / 88 (0.00%)   | 5 / 176 (2.84%)   | 1 / 177 (0.56%)   |
| occurrences (all)                | 0                | 5                 | 1                 |
| Arrhythmia supraventricular      |                  |                   |                   |
| subjects affected / exposed      | 0 / 88 (0.00%)   | 2 / 176 (1.14%)   | 3 / 177 (1.69%)   |
| occurrences (all)                | 0                | 5                 | 6                 |
| Arteriosclerosis coronary artery |                  |                   |                   |
| subjects affected / exposed      | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)                | 1                | 0                 | 0                 |
| Atrial fibrillation              |                  |                   |                   |
| subjects affected / exposed      | 13 / 88 (14.77%) | 28 / 176 (15.91%) | 31 / 177 (17.51%) |
| occurrences (all)                | 17               | 35                | 49                |
| Atrial flutter                   |                  |                   |                   |
| subjects affected / exposed      | 5 / 88 (5.68%)   | 8 / 176 (4.55%)   | 12 / 177 (6.78%)  |
| occurrences (all)                | 7                | 11                | 16                |
| Atrial tachycardia               |                  |                   |                   |
| subjects affected / exposed      | 3 / 88 (3.41%)   | 6 / 176 (3.41%)   | 7 / 177 (3.95%)   |
| occurrences (all)                | 5                | 6                 | 8                 |
| Atrial thrombosis                |                  |                   |                   |
| subjects affected / exposed      | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 4 / 177 (2.26%)   |
| occurrences (all)                | 1                | 1                 | 4                 |
| Atrioventricular block           |                  |                   |                   |
| subjects affected / exposed      | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                | 1                | 1                 | 0                 |
| Atrioventricular block complete  |                  |                   |                   |



|                                      |                  |                   |                   |
|--------------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed          | 0 / 88 (0.00%)   | 2 / 176 (1.14%)   | 3 / 177 (1.69%)   |
| occurrences (all)                    | 0                | 2                 | 3                 |
| Atrioventricular block first degree  |                  |                   |                   |
| subjects affected / exposed          | 2 / 88 (2.27%)   | 3 / 176 (1.70%)   | 2 / 177 (1.13%)   |
| occurrences (all)                    | 2                | 3                 | 2                 |
| Atrioventricular block second degree |                  |                   |                   |
| subjects affected / exposed          | 1 / 88 (1.14%)   | 2 / 176 (1.14%)   | 0 / 177 (0.00%)   |
| occurrences (all)                    | 1                | 2                 | 0                 |
| Bradyarrhythmia                      |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                    | 0                | 1                 | 0                 |
| Bradycardia                          |                  |                   |                   |
| subjects affected / exposed          | 1 / 88 (1.14%)   | 2 / 176 (1.14%)   | 3 / 177 (1.69%)   |
| occurrences (all)                    | 2                | 2                 | 3                 |
| Bundle branch block right            |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences (all)                    | 0                | 1                 | 2                 |
| Cardiac amyloidosis                  |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                    | 0                | 1                 | 0                 |
| Cardiac aneurysm                     |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                    | 0                | 0                 | 1                 |
| Cardiac disorder                     |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)                    | 0                | 1                 | 1                 |
| Cardiac failure                      |                  |                   |                   |
| subjects affected / exposed          | 18 / 88 (20.45%) | 20 / 176 (11.36%) | 33 / 177 (18.64%) |
| occurrences (all)                    | 35               | 29                | 62                |
| Cardiac failure acute                |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 3 / 176 (1.70%)   | 2 / 177 (1.13%)   |
| occurrences (all)                    | 0                | 3                 | 6                 |
| Cardiac failure chronic              |                  |                   |                   |
| subjects affected / exposed          | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                    | 0                | 0                 | 3                 |
| Cardiac failure congestive           |                  |                   |                   |

|                              |                |                 |                 |
|------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed  | 2 / 88 (2.27%) | 3 / 176 (1.70%) | 4 / 177 (2.26%) |
| occurrences (all)            | 2              | 3               | 5               |
| Cardiogenic shock            |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 1               | 1               |
| Cardiomegaly                 |                |                 |                 |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)            | 1              | 0               | 0               |
| Cardiomyopathy               |                |                 |                 |
| subjects affected / exposed  | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 2              | 0               | 1               |
| Cardiorenal syndrome         |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Coronary artery disease      |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)            | 0              | 2               | 0               |
| Cyanosis                     |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences (all)            | 0              | 1               | 3               |
| Diastolic dysfunction        |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Hepatojugular reflux         |                |                 |                 |
| subjects affected / exposed  | 2 / 88 (2.27%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)            | 2              | 4               | 1               |
| Intracardiac thrombus        |                |                 |                 |
| subjects affected / exposed  | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)            | 1              | 1               | 0               |
| Left ventricular dysfunction |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 1               | 1               |
| Left ventricular failure     |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)            | 0              | 1               | 2               |
| Low cardiac output syndrome  |                |                 |                 |

|                                |                |                 |                 |
|--------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed    | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)              | 0              | 0               | 2               |
| Mitral valve incompetence      |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 6 / 177 (3.39%) |
| occurrences (all)              | 1              | 2               | 7               |
| Palpitations                   |                |                 |                 |
| subjects affected / exposed    | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 8 / 177 (4.52%) |
| occurrences (all)              | 2              | 4               | 11              |
| Pericardial effusion           |                |                 |                 |
| subjects affected / exposed    | 2 / 88 (2.27%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences (all)              | 2              | 2               | 2               |
| Pulmonary valve incompetence   |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)              | 0              | 0               | 1               |
| Rhythm idioventricular         |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 0               | 0               |
| Right ventricular failure      |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 1               | 0               |
| Sinus arrest                   |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 1               | 0               |
| Sinus bradycardia              |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 1               | 0               |
| Supraventricular extrasystoles |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)              | 0              | 0               | 1               |
| Sinus node dysfunction         |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences (all)              | 0              | 1               | 3               |
| Tachyarrhythmia                |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)              | 2              | 0               | 0               |
| Supraventricular tachycardia   |                |                 |                 |

|                                |                |                 |                 |
|--------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed    | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)              | 0              | 2               | 1               |
| Tachycardia                    |                |                 |                 |
| subjects affected / exposed    | 3 / 88 (3.41%) | 6 / 176 (3.41%) | 1 / 177 (0.56%) |
| occurrences (all)              | 3              | 6               | 1               |
| Tricuspid valve incompetence   |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 4 / 177 (2.26%) |
| occurrences (all)              | 1              | 2               | 4               |
| Ventricular arrhythmia         |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)              | 0              | 1               | 1               |
| Ventricular extrasystoles      |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 3 / 177 (1.69%) |
| occurrences (all)              | 0              | 3               | 3               |
| Ventricular fibrillation       |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 0               | 0               |
| Ventricular tachycardia        |                |                 |                 |
| subjects affected / exposed    | 2 / 88 (2.27%) | 5 / 176 (2.84%) | 6 / 177 (3.39%) |
| occurrences (all)              | 3              | 8               | 6               |
| Nervous system disorders       |                |                 |                 |
| Ageusia                        |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 3 / 177 (1.69%) |
| occurrences (all)              | 0              | 2               | 4               |
| Altered state of consciousness |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 0               | 0               |
| Amnesia                        |                |                 |                 |
| subjects affected / exposed    | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 3 / 177 (1.69%) |
| occurrences (all)              | 2              | 4               | 3               |
| Anosmia                        |                |                 |                 |
| subjects affected / exposed    | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)              | 0              | 1               | 0               |
| Aphasia                        |                |                 |                 |
| subjects affected / exposed    | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)              | 1              | 1               | 0               |

|                             |                  |                   |                   |
|-----------------------------|------------------|-------------------|-------------------|
| Aphonia                     |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 0                 | 0                 |
| Asterixis                   |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 0                 | 0                 |
| Ataxia                      |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Balance disorder            |                  |                   |                   |
| subjects affected / exposed | 2 / 88 (2.27%)   | 15 / 176 (8.52%)  | 2 / 177 (1.13%)   |
| occurrences (all)           | 3                | 16                | 2                 |
| Brain injury                |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Burning sensation           |                  |                   |                   |
| subjects affected / exposed | 2 / 88 (2.27%)   | 2 / 176 (1.14%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 2                | 2                 | 0                 |
| Carotid artery aneurysm     |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Carpal tunnel syndrome      |                  |                   |                   |
| subjects affected / exposed | 5 / 88 (5.68%)   | 4 / 176 (2.27%)   | 4 / 177 (2.26%)   |
| occurrences (all)           | 5                | 4                 | 6                 |
| Cognitive disorder          |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 3 / 177 (1.69%)   |
| occurrences (all)           | 0                | 0                 | 3                 |
| Dementia                    |                  |                   |                   |
| subjects affected / exposed | 2 / 88 (2.27%)   | 1 / 176 (0.57%)   | 4 / 177 (2.26%)   |
| occurrences (all)           | 2                | 1                 | 4                 |
| Disturbance in attention    |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Dizziness                   |                  |                   |                   |
| subjects affected / exposed | 16 / 88 (18.18%) | 25 / 176 (14.20%) | 32 / 177 (18.08%) |
| occurrences (all)           | 20               | 31                | 36                |

|   |                     |                       |                        |
|---|---------------------|-----------------------|------------------------|
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)          | 0 / 88 (0.00%)<br>0 | 4 / 176 (2.27%)<br>5  | 7 / 177 (3.95%)<br>8   |
| Dysarthria<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0  | 1 / 177 (0.56%)<br>1   |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 88 (1.14%)<br>1 | 3 / 176 (1.70%)<br>3  | 4 / 177 (2.26%)<br>4   |
| Encephalopathy<br>subjects affected / exposed<br>occurrences (all)              | 0 / 88 (0.00%)<br>0 | 2 / 176 (1.14%)<br>2  | 2 / 177 (1.13%)<br>2   |
| Focal dyscognitive seizures<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0  | 1 / 177 (0.56%)<br>1   |
| Head discomfort<br>subjects affected / exposed<br>occurrences (all)             | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1  | 1 / 177 (0.56%)<br>1   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 88 (1.14%)<br>1 | 9 / 176 (5.11%)<br>11 | 11 / 177 (6.21%)<br>13 |
| Hemiparesis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1  | 0 / 177 (0.00%)<br>0   |
| Hypersomnia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0  | 2 / 177 (1.13%)<br>2   |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)               | 5 / 88 (5.68%)<br>5 | 4 / 176 (2.27%)<br>4  | 6 / 177 (3.39%)<br>6   |
| Hypotonia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1  | 0 / 177 (0.00%)<br>0   |
| Incoherent<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1  | 0 / 177 (0.00%)<br>0   |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Intention tremor            |                |                 |                 |
| subjects affected / exposed | 3 / 88 (3.41%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 3              | 1               | 0               |
| Lacunar infarction          |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Lethargy                    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 3 / 177 (1.69%) |
| occurrences (all)           | 0              | 3               | 3               |
| Loss of consciousness       |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 0               | 3               |
| Lumbar radiculopathy        |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 2               | 0               |
| Lumbosacral radiculopathy   |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Memory impairment           |                |                 |                 |
| subjects affected / exposed | 4 / 88 (4.55%) | 5 / 176 (2.84%) | 4 / 177 (2.26%) |
| occurrences (all)           | 5              | 5               | 4               |
| Mental impairment           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Myelopathy                  |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Nerve compression           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Neuralgia                   |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Neurodegenerative disorder  |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| Neuropathy peripheral       |                |                 |                  |
| subjects affected / exposed | 4 / 88 (4.55%) | 3 / 176 (1.70%) | 12 / 177 (6.78%) |
| occurrences (all)           | 4              | 4               | 14               |
| Orthostatic intolerance     |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Paraesthesia                |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 5 / 176 (2.84%) | 6 / 177 (3.39%)  |
| occurrences (all)           | 1              | 6               | 6                |
| Parkinson's disease         |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Parkinsonism                |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Parosmia                    |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Polyneuropathy              |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 1              | 2               | 2                |
| Poor quality sleep          |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Presyncope                  |                |                 |                  |
| subjects affected / exposed | 2 / 88 (2.27%) | 3 / 176 (1.70%) | 6 / 177 (3.39%)  |
| occurrences (all)           | 2              | 3               | 6                |
| Radiculopathy               |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Restless legs syndrome      |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 5 / 177 (2.82%)  |
| occurrences (all)           | 0              | 1               | 6                |
| Sciatica                    |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%)  |
| occurrences (all)           | 0              | 2               | 3                |



|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| Seizure                     |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Senile dementia             |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0                |
| Sensorimotor disorder       |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Somnolence                  |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 6 / 177 (3.39%)  |
| occurrences (all)           | 1              | 2               | 6                |
| Syncope                     |                |                 |                  |
| subjects affected / exposed | 5 / 88 (5.68%) | 5 / 176 (2.84%) | 11 / 177 (6.21%) |
| occurrences (all)           | 8              | 6               | 14               |
| Tension headache            |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0                |
| Tinel's sign                |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 0               | 1                |
| Toxic encephalopathy        |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Transient ischaemic attack  |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 0               | 1                |
| Tremor                      |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 8 / 177 (4.52%)  |
| occurrences (all)           | 0              | 0               | 8                |
| Tunnel vision               |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0                |
| Visual field defect         |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |

|                                      |                |                  |                  |
|--------------------------------------|----------------|------------------|------------------|
| Blood and lymphatic system disorders |                |                  |                  |
| Anaemia                              |                |                  |                  |
| subjects affected / exposed          | 5 / 88 (5.68%) | 10 / 176 (5.68%) | 13 / 177 (7.34%) |
| occurrences (all)                    | 5              | 10               | 13               |
| Anaemia macrocytic                   |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 0                | 1                |
| Coagulopathy                         |                |                  |                  |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 1              | 0                | 1                |
| Haemorrhagic disorder                |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0                |
| Heparin-induced thrombocytopenia     |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                    | 0              | 1                | 0                |
| Hypoprothrombinaemia                 |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 0                | 1                |
| Iron deficiency anaemia              |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 3 / 176 (1.70%)  | 3 / 177 (1.69%)  |
| occurrences (all)                    | 0              | 4                | 3                |
| Leukocytosis                         |                |                  |                  |
| subjects affected / exposed          | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 1              | 1                | 1                |
| Leukopenia                           |                |                  |                  |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 0              | 0                | 1                |
| Lymphadenopathy                      |                |                  |                  |
| subjects affected / exposed          | 2 / 88 (2.27%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences (all)                    | 2              | 1                | 1                |
| Macrocytosis                         |                |                  |                  |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 0 / 177 (0.00%)  |
| occurrences (all)                    | 1              | 0                | 0                |
| Microcytic anaemia                   |                |                  |                  |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Neutrophilia                |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Normocytic anaemia          |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Splenic infarction          |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Splenomegaly                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Thrombocytopenia            |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 6 / 176 (3.41%) | 5 / 177 (2.82%) |
| occurrences (all)           | 1              | 7               | 7               |
| Polycythaemia               |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Ear and labyrinth disorders |                |                 |                 |
| Cerumen impaction           |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)           | 1              | 1               | 2               |
| Deafness                    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 3               | 0               |
| Deafness neurosensory       |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Ear discomfort              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1               | 1               |
| Ear disorder                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| Ear haemorrhage<br>subjects affected / exposed<br>occurrences (all)              | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 2 / 177 (1.13%)<br>2 |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Eustachian tube dysfunction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Excessive cerumen production<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Hypoacusis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1 | 1 / 177 (0.56%)<br>1 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 1 / 177 (0.56%)<br>2 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 88 (1.14%)<br>1 | 5 / 176 (2.84%)<br>5 | 4 / 177 (2.26%)<br>5 |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all)           | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Eye disorders  |                     |                      |                      |
| Amaurosis fugax<br>subjects affected / exposed<br>occurrences (all)              | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>2 |
| Blepharitis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0 | 1 / 177 (0.56%)<br>2 |
| Blepharochalasis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1 | 0 / 177 (0.00%)<br>0 |
| Cataract   |                     |                      |                      |

|                              |                |                 |                 |
|------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed  | 3 / 88 (3.41%) | 8 / 176 (4.55%) | 2 / 177 (1.13%) |
| occurrences (all)            | 3              | 8               | 2               |
| Chalazion                    |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Conjunctival haemorrhage     |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)            | 0              | 2               | 0               |
| Diplopia                     |                |                 |                 |
| subjects affected / exposed  | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)            | 3              | 0               | 2               |
| Dry eye                      |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 5 / 177 (2.82%) |
| occurrences (all)            | 0              | 5               | 5               |
| Eye disorder                 |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 1               | 1               |
| Eye haemorrhage              |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)            | 0              | 1               | 3               |
| Eye oedema                   |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Eye pruritus                 |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)            | 0              | 1               | 0               |
| Eyelid bleeding              |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Eyelid cyst                  |                |                 |                 |
| subjects affected / exposed  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 0              | 0               | 1               |
| Glaucoma                     |                |                 |                 |
| subjects affected / exposed  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)            | 1              | 0               | 1               |
| Lacrimal structural disorder |                |                 |                 |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Lacrimation increased                        |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 1              | 1               | 0               |
| Macular degeneration                         |                |                 |                 |
| subjects affected / exposed                  | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 2              | 0               | 0               |
| Macular fibrosis                             |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Neovascular age-related macular degeneration |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 1              | 0               | 0               |
| Ocular hyperaemia                            |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Ocular vascular disorder                     |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Optic atrophy                                |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Papilloedema                                 |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 1              | 0               | 0               |
| Photopsia                                    |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 0              | 1               | 0               |
| Pterygium                                    |                |                 |                 |
| subjects affected / exposed                  | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                            | 0              | 0               | 2               |
| Retinal tear                                 |                |                 |                 |
| subjects affected / exposed                  | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                            | 1              | 1               | 0               |

|  |                     |                       |                      |
|--|---------------------|-----------------------|----------------------|
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)         | 2 / 88 (2.27%)<br>2 | 5 / 176 (2.84%)<br>5  | 3 / 177 (1.69%)<br>4 |
| Scleral discolouration<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0  | 1 / 177 (0.56%)<br>1 |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)  | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1  | 0 / 177 (0.00%)<br>0 |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)      | 2 / 88 (2.27%)<br>3 | 3 / 176 (1.70%)<br>4  | 1 / 177 (0.56%)<br>1 |
| Vitreous detachment<br>subjects affected / exposed<br>occurrences (all)    | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1  | 0 / 177 (0.00%)<br>0 |
| Gastrointestinal disorders   |                     |                       |                      |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)   | 3 / 88 (3.41%)<br>3 | 6 / 176 (3.41%)<br>6  | 7 / 177 (3.95%)<br>7 |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)   | 6 / 88 (6.82%)<br>6 | 7 / 176 (3.98%)<br>10 | 5 / 177 (2.82%)<br>5 |
| Abdominal hernia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0  | 1 / 177 (0.56%)<br>1 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)         | 3 / 88 (3.41%)<br>3 | 8 / 176 (4.55%)<br>8  | 6 / 177 (3.39%)<br>6 |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)   | 0 / 88 (0.00%)<br>0 | 2 / 176 (1.14%)<br>2  | 2 / 177 (1.13%)<br>2 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)   | 1 / 88 (1.14%)<br>1 | 5 / 176 (2.84%)<br>9  | 5 / 177 (2.82%)<br>7 |
| Abdominal wall haematoma   |                     |                       |                      |

|                             |                  |                   |                   |
|-----------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Abdominal rigidity          |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1                | 0                 | 0                 |
| Anal incontinence           |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 2 / 176 (1.14%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 2                 | 0                 |
| Ascites                     |                  |                   |                   |
| subjects affected / exposed | 7 / 88 (7.95%)   | 6 / 176 (3.41%)   | 9 / 177 (5.08%)   |
| occurrences (all)           | 12               | 7                 | 12                |
| Barrett's oesophagus        |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 2                 | 1                 |
| Bowel movement irregularity |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Colitis                     |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0                | 1                 | 0                 |
| Constipation                |                  |                   |                   |
| subjects affected / exposed | 14 / 88 (15.91%) | 25 / 176 (14.20%) | 30 / 177 (16.95%) |
| occurrences (all)           | 15               | 25                | 36                |
| Dental caries               |                  |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Diarrhoea                   |                  |                   |                   |
| subjects affected / exposed | 10 / 88 (11.36%) | 22 / 176 (12.50%) | 39 / 177 (22.03%) |
| occurrences (all)           | 11               | 25                | 52                |
| Diverticulum                |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences (all)           | 1                | 1                 | 2                 |
| Diverticulum intestinal     |                  |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%)   | 0 / 176 (0.00%)   | 3 / 177 (1.69%)   |
| occurrences (all)           | 1                | 0                 | 3                 |
| Dry mouth                   |                  |                   |                   |



|                                      |                |                 |                 |
|--------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed          | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 5 / 177 (2.82%) |
| occurrences (all)                    | 1              | 2               | 5               |
| Duodenal ulcer                       |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 1              | 0               | 0               |
| Dyspepsia                            |                |                 |                 |
| subjects affected / exposed          | 3 / 88 (3.41%) | 4 / 176 (2.27%) | 5 / 177 (2.82%) |
| occurrences (all)                    | 3              | 5               | 6               |
| Dysphagia                            |                |                 |                 |
| subjects affected / exposed          | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 2 / 177 (1.13%) |
| occurrences (all)                    | 2              | 4               | 3               |
| Enteritis                            |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 0              | 0               | 1               |
| Epigastric discomfort                |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 1              | 1               | 0               |
| Eruclation                           |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0               |
| Faeces soft                          |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                    | 1              | 0               | 1               |
| Flatulence                           |                |                 |                 |
| subjects affected / exposed          | 2 / 88 (2.27%) | 8 / 176 (4.55%) | 3 / 177 (1.69%) |
| occurrences (all)                    | 3              | 9               | 3               |
| Frequent bowel movements             |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 3               | 0               |
| Functional gastrointestinal disorder |                |                 |                 |
| subjects affected / exposed          | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                    | 0              | 1               | 0               |
| Gastric disorder                     |                |                 |                 |
| subjects affected / exposed          | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences (all)                    | 1              | 1               | 3               |
| Gastric ulcer                        |                |                 |                 |

|                                  |                |                 |                 |
|----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed      | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                | 0              | 1               | 1               |
| Gastritis                        |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 1 / 177 (0.56%) |
| occurrences (all)                | 0              | 3               | 2               |
| Gastritis haemorrhagic           |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)                | 0              | 2               | 0               |
| Gastrointestinal angiodysplasia  |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                | 0              | 1               | 0               |
| Gastrointestinal disorder        |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                | 0              | 0               | 1               |
| Gastrointestinal haemorrhage     |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                | 0              | 0               | 2               |
| Gastrooesophageal reflux disease |                |                 |                 |
| subjects affected / exposed      | 6 / 88 (6.82%) | 0 / 176 (0.00%) | 7 / 177 (3.95%) |
| occurrences (all)                | 6              | 0               | 7               |
| Gingival bleeding                |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                | 0              | 1               | 1               |
| Haematochezia                    |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                | 0              | 1               | 1               |
| Haemorrhoids                     |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 4 / 177 (2.26%) |
| occurrences (all)                | 0              | 5               | 4               |
| Hiatus hernia                    |                |                 |                 |
| subjects affected / exposed      | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 2 / 177 (1.13%) |
| occurrences (all)                | 1              | 2               | 2               |
| Ileus                            |                |                 |                 |
| subjects affected / exposed      | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                | 0              | 1               | 0               |
| Impaired gastric emptying        |                |                 |                 |

|                                    |                 |                   |                   |
|------------------------------------|-----------------|-------------------|-------------------|
| subjects affected / exposed        | 1 / 88 (1.14%)  | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                  | 1               | 1                 | 0                 |
| Incarcerated inguinal hernia       |                 |                   |                   |
| subjects affected / exposed        | 1 / 88 (1.14%)  | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)                  | 1               | 0                 | 0                 |
| Inguinal hernia                    |                 |                   |                   |
| subjects affected / exposed        | 5 / 88 (5.68%)  | 5 / 176 (2.84%)   | 3 / 177 (1.69%)   |
| occurrences (all)                  | 6               | 5                 | 3                 |
| Large intestine polyp              |                 |                   |                   |
| subjects affected / exposed        | 1 / 88 (1.14%)  | 1 / 176 (0.57%)   | 3 / 177 (1.69%)   |
| occurrences (all)                  | 1               | 1                 | 4                 |
| Lower gastrointestinal haemorrhage |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                  | 0               | 1                 | 0                 |
| Melaena                            |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)                  | 0               | 1                 | 1                 |
| Mouth haemorrhage                  |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)                  | 0               | 1                 | 0                 |
| Nausea                             |                 |                   |                   |
| subjects affected / exposed        | 9 / 88 (10.23%) | 20 / 176 (11.36%) | 36 / 177 (20.34%) |
| occurrences (all)                  | 11              | 21                | 53                |
| Oesophageal mass                   |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                  | 0               | 0                 | 1                 |
| Oesophageal spasm                  |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)                  | 0               | 0                 | 1                 |
| Oesophagitis                       |                 |                   |                   |
| subjects affected / exposed        | 0 / 88 (0.00%)  | 1 / 176 (0.57%)   | 2 / 177 (1.13%)   |
| occurrences (all)                  | 0               | 1                 | 2                 |
| Oral disorder                      |                 |                   |                   |
| subjects affected / exposed        | 1 / 88 (1.14%)  | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)                  | 1               | 0                 | 0                 |
| Pancreatic cyst                    |                 |                   |                   |

|                                   |                |                 |                 |
|-----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 1               | 1               |
| Pancreatic mass                   |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Periodontal disease               |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Pharyngo-oesophageal diverticulum |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Pneumatosis intestinalis          |                |                 |                 |
| subjects affected / exposed       | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 1              | 0               | 0               |
| Proctalgia                        |                |                 |                 |
| subjects affected / exposed       | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 2              | 0               | 0               |
| Rectal haemorrhage                |                |                 |                 |
| subjects affected / exposed       | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 1              | 2               | 0               |
| Rectal polyp                      |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Retching                          |                |                 |                 |
| subjects affected / exposed       | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                 | 1              | 0               | 2               |
| Salivary gland calculus           |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 0               | 1               |
| Salivary gland enlargement        |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 0               | 1               |
| Tooth loss                        |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 0               | 1               |
| Toothache                         |                |                 |                 |

|  |                |                 |                  |
|--|----------------|-----------------|------------------|
| subjects affected / exposed            | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%)  |
| occurrences (all)                      | 0              | 2               | 2                |
| Umbilical hernia                       |                |                 |                  |
| subjects affected / exposed            | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%)  |
| occurrences (all)                      | 1              | 0               | 2                |
| Upper gastrointestinal haemorrhage     |                |                 |                  |
| subjects affected / exposed            | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)                      | 0              | 1               | 0                |
| Vomiting                               |                |                 |                  |
| subjects affected / exposed            | 7 / 88 (7.95%) | 6 / 176 (3.41%) | 16 / 177 (9.04%) |
| occurrences (all)                      | 7              | 6               | 19               |
| Skin and subcutaneous tissue disorders |                |                 |                  |
| Acne                                   |                |                 |                  |
| subjects affected / exposed            | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)                      | 0              | 0               | 1                |
| Actinic keratosis                      |                |                 |                  |
| subjects affected / exposed            | 3 / 88 (3.41%) | 3 / 176 (1.70%) | 0 / 177 (0.00%)  |
| occurrences (all)                      | 3              | 3               | 0                |
| Alopecia                               |                |                 |                  |
| subjects affected / exposed            | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 0 / 177 (0.00%)  |
| occurrences (all)                      | 0              | 3               | 0                |
| Blister                                |                |                 |                  |
| subjects affected / exposed            | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 2 / 177 (1.13%)  |
| occurrences (all)                      | 0              | 2               | 3                |
| Cold sweat                             |                |                 |                  |
| subjects affected / exposed            | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)                      | 1              | 0               | 0                |
| Decubitus ulcer                        |                |                 |                  |
| subjects affected / exposed            | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 4 / 177 (2.26%)  |
| occurrences (all)                      | 1              | 0               | 4                |
| Dermatitis                             |                |                 |                  |
| subjects affected / exposed            | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)                      | 1              | 0               | 1                |
| Dermatitis allergic                    |                |                 |                  |
| subjects affected / exposed            | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)                      | 0              | 1               | 2                |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Dermatitis atopic           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 2               | 0               |
| Dermatitis contact          |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 2               | 1               |
| Diabetic foot               |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Dry skin                    |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 1               | 0               |
| Ecchymosis                  |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 3 / 177 (1.69%) |
| occurrences (all)           | 0              | 6               | 3               |
| Eczema                      |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 1               | 1               |
| Eczema nummular             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 2               | 0               |
| Erythema                    |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%) | 5 / 177 (2.82%) |
| occurrences (all)           | 1              | 2               | 5               |
| Haemorrhage subcutaneous    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Hair colour changes         |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Hyperhidrosis               |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 0 / 177 (0.00%) |
| occurrences (all)           | 2              | 5               | 0               |
| Hyperkeratosis              |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 1              | 0               | 1               |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Hypertrophic scar           |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Ingrowing nail              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Lentigo                     |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Myxoid cyst                 |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Nail dystrophy              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Nail ridging                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Neurodermatitis             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Night sweats                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Onychomalacia               |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Petechiae                   |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Photodermatitis             |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1               | 1               |
| Pigmentation disorder       |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |

|                                       |                |                  |                  |
|---------------------------------------|----------------|------------------|------------------|
| Post inflammatory pigmentation change |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                     | 0              | 1                | 0                |
| Pruritus                              |                |                  |                  |
| subjects affected / exposed           | 4 / 88 (4.55%) | 12 / 176 (6.82%) | 15 / 177 (8.47%) |
| occurrences (all)                     | 5              | 14               | 16               |
| Pruritus generalised                  |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 2 / 177 (1.13%)  |
| occurrences (all)                     | 0              | 1                | 2                |
| Psoriasis                             |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0                | 1                |
| Purpura                               |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0                | 1                |
| Rash                                  |                |                  |                  |
| subjects affected / exposed           | 3 / 88 (3.41%) | 6 / 176 (3.41%)  | 12 / 177 (6.78%) |
| occurrences (all)                     | 3              | 6                | 16               |
| Rash erythematous                     |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)  |
| occurrences (all)                     | 0              | 2                | 0                |
| Rash pruritic                         |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0                | 1                |
| Seborrhoeic dermatitis                |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0                | 1                |
| Skin atrophy                          |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)                     | 0              | 1                | 0                |
| Skin disorder                         |                |                  |                  |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)                     | 0              | 0                | 1                |
| Skin lesion                           |                |                  |                  |



|                                   |                |                 |                   |
|-----------------------------------|----------------|-----------------|-------------------|
| subjects affected / exposed       | 0 / 88 (0.00%) | 4 / 176 (2.27%) | 4 / 177 (2.26%)   |
| occurrences (all)                 | 0              | 4               | 5                 |
| Skin ulcer                        |                |                 |                   |
| subjects affected / exposed       | 3 / 88 (3.41%) | 7 / 176 (3.98%) | 1 / 177 (0.56%)   |
| occurrences (all)                 | 3              | 9               | 1                 |
| Stasis dermatitis                 |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 2               | 0                 |
| Subcutaneous emphysema            |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 1               | 0                 |
| Swelling face                     |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 1               | 0                 |
| Transient acantholytic dermatosis |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 2               | 0                 |
| Xanthoma                          |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 0               | 1                 |
| Papule                            |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 0              | 1               | 0                 |
| Xeroderma                         |                |                 |                   |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)   |
| occurrences (all)                 | 0              | 1               | 1                 |
| Urticaria                         |                |                 |                   |
| subjects affected / exposed       | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 1              | 1               | 0                 |
| Renal and urinary disorders       |                |                 |                   |
| Acute kidney injury               |                |                 |                   |
| subjects affected / exposed       | 5 / 88 (5.68%) | 8 / 176 (4.55%) | 18 / 177 (10.17%) |
| occurrences (all)                 | 6              | 11              | 19                |
| Azotaemia                         |                |                 |                   |
| subjects affected / exposed       | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)   |
| occurrences (all)                 | 1              | 1               | 0                 |

|                             |                  |                 |                  |
|-----------------------------|------------------|-----------------|------------------|
| Calculus bladder            |                  |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%)   | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 1                | 1               | 0                |
| Chronic kidney disease      |                  |                 |                  |
| subjects affected / exposed | 4 / 88 (4.55%)   | 6 / 176 (3.41%) | 6 / 177 (3.39%)  |
| occurrences (all)           | 4                | 7               | 7                |
| Dysuria                     |                  |                 |                  |
| subjects affected / exposed | 2 / 88 (2.27%)   | 1 / 176 (0.57%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 3                | 1               | 3                |
| End stage renal disease     |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0                |
| Haematuria                  |                  |                 |                  |
| subjects affected / exposed | 10 / 88 (11.36%) | 8 / 176 (4.55%) | 15 / 177 (8.47%) |
| occurrences (all)           | 13               | 9               | 17               |
| Incontinence                |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0                |
| Micturition urgency         |                  |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%)   | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 1                | 1               | 0                |
| Nephrolithiasis             |                  |                 |                  |
| subjects affected / exposed | 2 / 88 (2.27%)   | 1 / 176 (0.57%) | 3 / 177 (1.69%)  |
| occurrences (all)           | 2                | 1               | 3                |
| Neurogenic bladder          |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0                | 1               | 1                |
| Nocturia                    |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0                | 1               | 0                |
| Oliguria                    |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0                | 0               | 1                |
| Pollakiuria                 |                  |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%)   | 0 / 176 (0.00%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 0                | 0               | 2                |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| Polyuria                    |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 0               | 2               |
| Proteinuria                 |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 5 / 177 (2.82%) |
| occurrences (all)           | 0              | 2               | 5               |
| Renal cyst                  |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 4 / 176 (2.27%) | 2 / 177 (1.13%) |
| occurrences (all)           | 1              | 4               | 2               |
| Renal disorder              |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Renal failure               |                |                 |                 |
| subjects affected / exposed | 5 / 88 (5.68%) | 8 / 176 (4.55%) | 7 / 177 (3.95%) |
| occurrences (all)           | 6              | 10              | 7               |
| Renal impairment            |                |                 |                 |
| subjects affected / exposed | 2 / 88 (2.27%) | 5 / 176 (2.84%) | 8 / 177 (4.52%) |
| occurrences (all)           | 2              | 5               | 8               |
| Renal infarct               |                |                 |                 |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)           | 1              | 0               | 0               |
| Renal injury                |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)           | 0              | 0               | 2               |
| Renal mass                  |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Stress urinary incontinence |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)           | 0              | 1               | 0               |
| Ureterolithiasis            |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 0               | 1               |
| Urinary bladder polyp       |                |                 |                 |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%) |
| occurrences (all)           | 0              | 1               | 1               |

|   |                     |                        |                        |
|---|---------------------|------------------------|------------------------|
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)          | 1 / 88 (1.14%)<br>1 | 2 / 176 (1.14%)<br>2   | 2 / 177 (1.13%)<br>2   |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)             | 2 / 88 (2.27%)<br>2 | 6 / 176 (3.41%)<br>6   | 12 / 177 (6.78%)<br>12 |
| Urinary tract pain<br>subjects affected / exposed<br>occurrences (all)            | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1   | 0 / 177 (0.00%)<br>0   |
| Urine flow decreased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 88 (0.00%)<br>0 | 1 / 176 (0.57%)<br>1   | 0 / 177 (0.00%)<br>0   |
| Urethral stenosis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Endocrine disorders   |                     |                        |                        |
| Hyperparathyroidism<br>subjects affected / exposed<br>occurrences (all)           | 1 / 88 (1.14%)<br>1 | 0 / 176 (0.00%)<br>0   | 2 / 177 (1.13%)<br>2   |
| Hyperparathyroidism secondary<br>subjects affected / exposed<br>occurrences (all) | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)               | 0 / 88 (0.00%)<br>0 | 3 / 176 (1.70%)<br>3   | 2 / 177 (1.13%)<br>2   |
| Hypogonadism<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 88 (0.00%)<br>0 | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                | 5 / 88 (5.68%)<br>6 | 12 / 176 (6.82%)<br>12 | 10 / 177 (5.65%)<br>10 |
| Thyroid mass<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>1   | 1 / 177 (0.56%)<br>1   |
| Musculoskeletal and connective tissue disorders                                   |                     |                        |                        |

|                                 |                 |                  |                   |
|---------------------------------|-----------------|------------------|-------------------|
| Arthralgia                      |                 |                  |                   |
| subjects affected / exposed     | 8 / 88 (9.09%)  | 17 / 176 (9.66%) | 20 / 177 (11.30%) |
| occurrences (all)               | 11              | 19               | 27                |
| Arthritis                       |                 |                  |                   |
| subjects affected / exposed     | 4 / 88 (4.55%)  | 4 / 176 (2.27%)  | 1 / 177 (0.56%)   |
| occurrences (all)               | 4               | 4                | 1                 |
| Back pain                       |                 |                  |                   |
| subjects affected / exposed     | 9 / 88 (10.23%) | 17 / 176 (9.66%) | 23 / 177 (12.99%) |
| occurrences (all)               | 9               | 18               | 29                |
| Bone pain                       |                 |                  |                   |
| subjects affected / exposed     | 1 / 88 (1.14%)  | 0 / 176 (0.00%)  | 0 / 177 (0.00%)   |
| occurrences (all)               | 1               | 0                | 0                 |
| Bursitis                        |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 3 / 176 (1.70%)  | 3 / 177 (1.69%)   |
| occurrences (all)               | 0               | 6                | 3                 |
| Chest wall haematoma            |                 |                  |                   |
| subjects affected / exposed     | 1 / 88 (1.14%)  | 0 / 176 (0.00%)  | 0 / 177 (0.00%)   |
| occurrences (all)               | 1               | 0                | 0                 |
| Chondrocalcinosis               |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)               | 0               | 1                | 1                 |
| Chondrocalcinosis pyrophosphate |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 3 / 176 (1.70%)  | 0 / 177 (0.00%)   |
| occurrences (all)               | 0               | 5                | 0                 |
| Enthesopathy                    |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)               | 0               | 0                | 1                 |
| Exostosis                       |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)               | 0               | 1                | 0                 |
| Flank pain                      |                 |                  |                   |
| subjects affected / exposed     | 0 / 88 (0.00%)  | 0 / 176 (0.00%)  | 3 / 177 (1.69%)   |
| occurrences (all)               | 0               | 0                | 5                 |
| Foot deformity                  |                 |                  |                   |
| subjects affected / exposed     | 1 / 88 (1.14%)  | 1 / 176 (0.57%)  | 2 / 177 (1.13%)   |
| occurrences (all)               | 1               | 1                | 3                 |

|                                     |                |                 |                 |
|-------------------------------------|----------------|-----------------|-----------------|
| Fracture pain                       |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 0              | 1               | 0               |
| Gouty tophus                        |                |                 |                 |
| subjects affected / exposed         | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 1              | 0               | 0               |
| Groin pain                          |                |                 |                 |
| subjects affected / exposed         | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 4 / 177 (2.26%) |
| occurrences (all)                   | 1              | 0               | 4               |
| Haemarthrosis                       |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%) |
| occurrences (all)                   | 0              | 1               | 3               |
| Intervertebral disc degeneration    |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 2               | 1               |
| Intervertebral disc protrusion      |                |                 |                 |
| subjects affected / exposed         | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 1              | 0               | 0               |
| Intervertebral disc space narrowing |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Joint swelling                      |                |                 |                 |
| subjects affected / exposed         | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 5 / 177 (2.82%) |
| occurrences (all)                   | 2              | 0               | 7               |
| Knee deformity                      |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 0              | 1               | 0               |
| Limb discomfort                     |                |                 |                 |
| subjects affected / exposed         | 2 / 88 (2.27%) | 4 / 176 (2.27%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 2              | 4               | 1               |
| Lumbar spinal stenosis              |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 3 / 176 (1.70%) | 2 / 177 (1.13%) |
| occurrences (all)                   | 0              | 5               | 2               |
| Metatarsalgia                       |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 0              | 1               | 0               |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| Muscle atrophy<br>subjects affected / exposed<br>occurrences (all)             | 2 / 88 (2.27%)<br>2    | 2 / 176 (1.14%)<br>3   | 5 / 177 (2.82%)<br>5   |
| Muscle contracture<br>subjects affected / exposed<br>occurrences (all)         | 0 / 88 (0.00%)<br>0    | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)              | 10 / 88 (11.36%)<br>13 | 15 / 176 (8.52%)<br>15 | 14 / 177 (7.91%)<br>19 |
| Muscle twitching<br>subjects affected / exposed<br>occurrences (all)           | 0 / 88 (0.00%)<br>0    | 0 / 176 (0.00%)<br>0   | 1 / 177 (0.56%)<br>1   |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)          | 2 / 88 (2.27%)<br>2    | 5 / 176 (2.84%)<br>8   | 12 / 177 (6.78%)<br>12 |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1    | 3 / 176 (1.70%)<br>3   | 3 / 177 (1.69%)<br>3   |
| Musculoskeletal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1    | 1 / 176 (0.57%)<br>1   | 4 / 177 (2.26%)<br>5   |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 3 / 88 (3.41%)<br>4    | 13 / 176 (7.39%)<br>17 | 11 / 177 (6.21%)<br>12 |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)  | 2 / 88 (2.27%)<br>2    | 3 / 176 (1.70%)<br>3   | 1 / 177 (0.56%)<br>1   |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 5 / 88 (5.68%)<br>7    | 5 / 176 (2.84%)<br>5   | 2 / 177 (1.13%)<br>2   |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 88 (4.55%)<br>4    | 3 / 176 (1.70%)<br>3   | 5 / 177 (2.82%)<br>5   |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)             | 2 / 88 (2.27%)<br>2    | 9 / 176 (5.11%)<br>10  | 6 / 177 (3.39%)<br>7   |

|                             |                |                   |                   |
|-----------------------------|----------------|-------------------|-------------------|
| Osteopenia                  |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0              | 0                 | 1                 |
| Osteoporosis                |                |                   |                   |
| subjects affected / exposed | 2 / 88 (2.27%) | 1 / 176 (0.57%)   | 3 / 177 (1.69%)   |
| occurrences (all)           | 2              | 1                 | 3                 |
| Pain in extremity           |                |                   |                   |
| subjects affected / exposed | 6 / 88 (6.82%) | 27 / 176 (15.34%) | 20 / 177 (11.30%) |
| occurrences (all)           | 7              | 32                | 25                |
| Pain in jaw                 |                |                   |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 1              | 0                 | 0                 |
| Plantar fasciitis           |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 2                 | 0                 |
| Polymyalgia rheumatica      |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 1                 | 0                 |
| Psoriatic arthropathy       |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0              | 0                 | 1                 |
| Rotator cuff syndrome       |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 5 / 176 (2.84%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 7                 | 0                 |
| Spinal column stenosis      |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 2                 | 0                 |
| Spinal osteoarthritis       |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 3 / 176 (1.70%)   | 2 / 177 (1.13%)   |
| occurrences (all)           | 0              | 3                 | 2                 |
| Spondylolisthesis           |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0              | 3                 | 1                 |
| Synovial cyst               |                |                   |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)           | 0              | 2                 | 1                 |



|                               |                |                   |                   |
|-------------------------------|----------------|-------------------|-------------------|
| Tendonitis                    |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 2 / 176 (1.14%)   | 4 / 177 (2.26%)   |
| occurrences (all)             | 0              | 2                 | 5                 |
| Tenosynovitis                 |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 0                 | 1                 |
| Trigger finger                |                |                   |                   |
| subjects affected / exposed   | 1 / 88 (1.14%) | 1 / 176 (0.57%)   | 0 / 177 (0.00%)   |
| occurrences (all)             | 1              | 1                 | 0                 |
| Infections and infestations   |                |                   |                   |
| Acute sinusitis               |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 2 / 176 (1.14%)   | 2 / 177 (1.13%)   |
| occurrences (all)             | 0              | 3                 | 3                 |
| Arthritis bacterial           |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 0                 | 1                 |
| Bacteraemia                   |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 0                 | 1                 |
| Bacterial infection           |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 1                 | 1                 |
| Bacterial abdominal infection |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 0                 | 1                 |
| Body tinea                    |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 1 / 176 (0.57%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 1                 | 1                 |
| Bronchiolitis                 |                |                   |                   |
| subjects affected / exposed   | 0 / 88 (0.00%) | 0 / 176 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences (all)             | 0              | 0                 | 1                 |
| Bronchitis                    |                |                   |                   |
| subjects affected / exposed   | 7 / 88 (7.95%) | 21 / 176 (11.93%) | 19 / 177 (10.73%) |
| occurrences (all)             | 8              | 24                | 20                |
| Candida infection             |                |                   |                   |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 2               | 0                |
| Candiduria                  |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Cellulitis                  |                |                 |                  |
| subjects affected / exposed | 6 / 88 (6.82%) | 6 / 176 (3.41%) | 10 / 177 (5.65%) |
| occurrences (all)           | 6              | 6               | 11               |
| Chronic sinusitis           |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Conjunctivitis              |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 0              | 1               | 2                |
| Cystitis                    |                |                 |                  |
| subjects affected / exposed | 2 / 88 (2.27%) | 5 / 176 (2.84%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 2              | 5               | 0                |
| Device related infection    |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 1               | 1                |
| Diverticulitis              |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 1               | 1                |
| Ear infection               |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 2               | 1                |
| Endocarditis                |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0                |
| Enteritis infectious        |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Enterococcal bacteraemia    |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Erysipelas                  |                |                 |                  |

|                                     |                |                 |                 |
|-------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed         | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%) |
| occurrences (all)                   | 0              | 1               | 2               |
| Escherichia urinary tract infection |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 0              | 2               | 0               |
| Eye infection                       |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 2               | 1               |
| Folliculitis                        |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Fungal infection                    |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Fungal skin infection               |                |                 |                 |
| subjects affected / exposed         | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                   | 2              | 0               | 2               |
| Gas gangrene                        |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Gastritis viral                     |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Gastroenteritis                     |                |                 |                 |
| subjects affected / exposed         | 1 / 88 (1.14%) | 5 / 176 (2.84%) | 3 / 177 (1.69%) |
| occurrences (all)                   | 1              | 5               | 4               |
| Gastroenteritis viral               |                |                 |                 |
| subjects affected / exposed         | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                   | 1              | 0               | 0               |
| Gastrointestinal infection          |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 3 / 177 (1.69%) |
| occurrences (all)                   | 0              | 0               | 3               |
| Gastrointestinal viral infection    |                |                 |                 |
| subjects affected / exposed         | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                   | 0              | 0               | 1               |
| Genitourinary tract infection       |                |                 |                 |

|                                   |                |                 |                 |
|-----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed       | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 3 / 177 (1.69%) |
| occurrences (all)                 | 1              | 0               | 5               |
| Helicobacter gastritis            |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 0               | 1               |
| Herpes zoster                     |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 6 / 176 (3.41%) | 6 / 177 (3.39%) |
| occurrences (all)                 | 0              | 9               | 7               |
| Hordeolum                         |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 2               | 1               |
| Impetigo                          |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Infected cyst                     |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Infected dermal cyst              |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Infected skin ulcer               |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%) |
| occurrences (all)                 | 0              | 0               | 1               |
| Influenza                         |                |                 |                 |
| subjects affected / exposed       | 4 / 88 (4.55%) | 7 / 176 (3.98%) | 6 / 177 (3.39%) |
| occurrences (all)                 | 5              | 8               | 6               |
| Kidney infection                  |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 0              | 1               | 0               |
| Labyrinthitis                     |                |                 |                 |
| subjects affected / exposed       | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 2 / 177 (1.13%) |
| occurrences (all)                 | 0              | 0               | 2               |
| Localised infection               |                |                 |                 |
| subjects affected / exposed       | 2 / 88 (2.27%) | 0 / 176 (0.00%) | 0 / 177 (0.00%) |
| occurrences (all)                 | 2              | 0               | 0               |
| Lower respiratory tract infection |                |                 |                 |

|                             |                |                  |                  |
|-----------------------------|----------------|------------------|------------------|
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 3 / 177 (1.69%)  |
| occurrences (all)           | 0              | 0                | 4                |
| Lung infection              |                |                  |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)           | 2              | 1                | 0                |
| Molluscum contagiosum       |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0                |
| Nasopharyngitis             |                |                  |                  |
| subjects affected / exposed | 7 / 88 (7.95%) | 14 / 176 (7.95%) | 17 / 177 (9.60%) |
| occurrences (all)           | 9              | 17               | 23               |
| Oesophageal candidiasis     |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0                | 1                |
| Onychomycosis               |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 2 / 177 (1.13%)  |
| occurrences (all)           | 0              | 0                | 2                |
| Oral candidiasis            |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 1                | 1                |
| Parotitis                   |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0                | 1                |
| Periodontitis               |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1                | 0                |
| Periorbital cellulitis      |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0                | 1                |
| Pharyngitis                 |                |                  |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 1                | 1                |
| Pneumonia                   |                |                  |                  |
| subjects affected / exposed | 4 / 88 (4.55%) | 12 / 176 (6.82%) | 7 / 177 (3.95%)  |
| occurrences (all)           | 7              | 15               | 8                |
| Pneumonia bacterial         |                |                  |                  |

|                                       |                |                  |                 |
|---------------------------------------|----------------|------------------|-----------------|
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)                     | 0              | 1                | 0               |
| Pneumonia viral                       |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)                     | 0              | 1                | 0               |
| Post procedural infection             |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%) |
| occurrences (all)                     | 0              | 2                | 0               |
| Pulpitis dental                       |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)                     | 0              | 0                | 1               |
| Pyelonephritis                        |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)                     | 0              | 1                | 0               |
| Pyuria                                |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)                     | 0              | 0                | 1               |
| Respiratory syncytial virus infection |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%) |
| occurrences (all)                     | 0              | 0                | 1               |
| Respiratory tract infection           |                |                  |                 |
| subjects affected / exposed           | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 2 / 177 (1.13%) |
| occurrences (all)                     | 1              | 1                | 2               |
| Rhinitis                              |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 1 / 177 (0.56%) |
| occurrences (all)                     | 0              | 2                | 1               |
| Sepsis                                |                |                  |                 |
| subjects affected / exposed           | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%) |
| occurrences (all)                     | 1              | 1                | 1               |
| Septic shock                          |                |                  |                 |
| subjects affected / exposed           | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%) |
| occurrences (all)                     | 0              | 1                | 0               |
| Sinusitis                             |                |                  |                 |
| subjects affected / exposed           | 4 / 88 (4.55%) | 10 / 176 (5.68%) | 1 / 177 (0.56%) |
| occurrences (all)                     | 4              | 12               | 1               |
| Skin infection                        |                |                  |                 |

|   |                |                  |                   |
|---|----------------|------------------|-------------------|
| subjects affected / exposed             | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0              | 2                | 0                 |
| Staphylococcal sepsis                   |                |                  |                   |
| subjects affected / exposed             | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 1              | 0                | 0                 |
| Tooth abscess                           |                |                  |                   |
| subjects affected / exposed             | 2 / 88 (2.27%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)                       | 3              | 1                | 1                 |
| Tooth infection                         |                |                  |                   |
| subjects affected / exposed             | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)                       | 0              | 1                | 1                 |
| Tracheitis                              |                |                  |                   |
| subjects affected / exposed             | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0              | 1                | 0                 |
| Tracheobronchitis                       |                |                  |                   |
| subjects affected / exposed             | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0              | 2                | 0                 |
| Upper respiratory tract infection       |                |                  |                   |
| subjects affected / exposed             | 7 / 88 (7.95%) | 17 / 176 (9.66%) | 16 / 177 (9.04%)  |
| occurrences (all)                       | 7              | 19               | 18                |
| Urinary tract infection                 |                |                  |                   |
| subjects affected / exposed             | 7 / 88 (7.95%) | 15 / 176 (8.52%) | 25 / 177 (14.12%) |
| occurrences (all)                       | 10             | 18               | 33                |
| Varicella zoster virus infection        |                |                  |                   |
| subjects affected / exposed             | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 1              | 0                | 0                 |
| Viral infection                         |                |                  |                   |
| subjects affected / exposed             | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0              | 2                | 0                 |
| Viral upper respiratory tract infection |                |                  |                   |
| subjects affected / exposed             | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)                       | 1              | 1                | 1                 |
| Wound infection                         |                |                  |                   |
| subjects affected / exposed             | 0 / 88 (0.00%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)   |
| occurrences (all)                       | 0              | 2                | 0                 |
| Gingivitis                              |                |                  |                   |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 88 (1.14%)<br>1 | 1 / 176 (0.57%)<br>2 | 1 / 177 (0.56%)<br>1 |
| Metabolism and nutrition disorders               |                     |                      |                      |
| Adult failure to thrive                          |                     |                      |                      |
| subjects affected / exposed                      | 0 / 88 (0.00%)      | 0 / 176 (0.00%)      | 1 / 177 (0.56%)      |
| occurrences (all)                                | 0                   | 0                    | 1                    |
| Cachexia   |                     |                      |                      |
| subjects affected / exposed                      | 3 / 88 (3.41%)      | 1 / 176 (0.57%)      | 3 / 177 (1.69%)      |
| occurrences (all)                                | 3                   | 2                    | 3                    |
| Decreased appetite                               |                     |                      |                      |
| subjects affected / exposed                      | 8 / 88 (9.09%)      | 14 / 176 (7.95%)     | 25 / 177 (14.12%)    |
| occurrences (all)                                | 9                   | 15                   | 25                   |
| Dehydration                                      |                     |                      |                      |
| subjects affected / exposed                      | 3 / 88 (3.41%)      | 4 / 176 (2.27%)      | 4 / 177 (2.26%)      |
| occurrences (all)                                | 3                   | 4                    | 4                    |
| Diabetes mellitus                                |                     |                      |                      |
| subjects affected / exposed                      | 1 / 88 (1.14%)      | 1 / 176 (0.57%)      | 5 / 177 (2.82%)      |
| occurrences (all)                                | 1                   | 1                    | 5                    |
| Diabetes mellitus inadequate control             |                     |                      |                      |
| subjects affected / exposed                      | 0 / 88 (0.00%)      | 0 / 176 (0.00%)      | 2 / 177 (1.13%)      |
| occurrences (all)                                | 0                   | 0                    | 2                    |
| Fluid overload                                   |                     |                      |                      |
| subjects affected / exposed                      | 11 / 88 (12.50%)    | 18 / 176 (10.23%)    | 27 / 177 (15.25%)    |
| occurrences (all)                                | 12                  | 31                   | 44                   |
| Fluid retention                                  |                     |                      |                      |
| subjects affected / exposed                      | 3 / 88 (3.41%)      | 5 / 176 (2.84%)      | 15 / 177 (8.47%)     |
| occurrences (all)                                | 5                   | 7                    | 18                   |
| Gout   |                     |                      |                      |
| subjects affected / exposed                      | 10 / 88 (11.36%)    | 17 / 176 (9.66%)     | 29 / 177 (16.38%)    |
| occurrences (all)                                | 10                  | 22                   | 34                   |
| Hyperammonaemia                                  |                     |                      |                      |
| subjects affected / exposed                      | 0 / 88 (0.00%)      | 0 / 176 (0.00%)      | 1 / 177 (0.56%)      |
| occurrences (all)                                | 0                   | 0                    | 1                    |
| Hypercalcaemia                                   |                     |                      |                      |
| subjects affected / exposed                      | 0 / 88 (0.00%)      | 0 / 176 (0.00%)      | 2 / 177 (1.13%)      |
| occurrences (all)                                | 0                   | 0                    | 2                    |



|                             |                |                  |                   |
|-----------------------------|----------------|------------------|-------------------|
| Hyperglycaemia              |                |                  |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%)  | 3 / 177 (1.69%)   |
| occurrences (all)           | 1              | 2                | 3                 |
| Hyperkalaemia               |                |                  |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 8 / 176 (4.55%)  | 10 / 177 (5.65%)  |
| occurrences (all)           | 1              | 10               | 10                |
| Hyperlactacidaemia          |                |                  |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 1                | 0                 |
| Hyperlipidaemia             |                |                  |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%)  | 1 / 177 (0.56%)   |
| occurrences (all)           | 0              | 0                | 1                 |
| Hyperuricaemia              |                |                  |                   |
| subjects affected / exposed | 3 / 88 (3.41%) | 9 / 176 (5.11%)  | 7 / 177 (3.95%)   |
| occurrences (all)           | 3              | 10               | 7                 |
| Hypervolaemia               |                |                  |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 2 / 176 (1.14%)  | 0 / 177 (0.00%)   |
| occurrences (all)           | 1              | 3                | 0                 |
| Hypoalbuminaemia            |                |                  |                   |
| subjects affected / exposed | 2 / 88 (2.27%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)           | 2              | 1                | 1                 |
| Hypocalcaemia               |                |                  |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 0 / 177 (0.00%)   |
| occurrences (all)           | 0              | 1                | 0                 |
| Hypochloraemia              |                |                  |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%)  | 0 / 177 (0.00%)   |
| occurrences (all)           | 1              | 0                | 0                 |
| Hypoglycaemia               |                |                  |                   |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%)  | 2 / 177 (1.13%)   |
| occurrences (all)           | 0              | 1                | 3                 |
| Hypokalaemia                |                |                  |                   |
| subjects affected / exposed | 8 / 88 (9.09%) | 14 / 176 (7.95%) | 19 / 177 (10.73%) |
| occurrences (all)           | 8              | 15               | 28                |
| Hypomagnesaemia             |                |                  |                   |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 176 (0.57%)  | 1 / 177 (0.56%)   |
| occurrences (all)           | 1              | 1                | 1                 |

|                             |                |                 |                  |
|-----------------------------|----------------|-----------------|------------------|
| Hyponatraemia               |                |                 |                  |
| subjects affected / exposed | 2 / 88 (2.27%) | 8 / 176 (4.55%) | 10 / 177 (5.65%) |
| occurrences (all)           | 3              | 8               | 12               |
| Hypoproteinaemia            |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 0               | 1                |
| Hypovolaemia                |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 0               | 1                |
| Iron deficiency             |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 0              | 1               | 2                |
| Malnutrition                |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 2 / 176 (1.14%) | 3 / 177 (1.69%)  |
| occurrences (all)           | 0              | 2               | 3                |
| Metabolic acidosis          |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 3 / 177 (1.69%)  |
| occurrences (all)           | 0              | 1               | 3                |
| Metabolic alkalosis         |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Metabolic disorder          |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 176 (0.57%) | 0 / 177 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0                |
| Protein deficiency          |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 1                |
| Type 2 diabetes mellitus    |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 2 / 177 (1.13%)  |
| occurrences (all)           | 1              | 0               | 2                |
| Vitamin B12 deficiency      |                |                 |                  |
| subjects affected / exposed | 0 / 88 (0.00%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 0              | 0               | 4                |
| Vitamin D deficiency        |                |                 |                  |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 176 (0.00%) | 1 / 177 (0.56%)  |
| occurrences (all)           | 1              | 0               | 1                |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 16 April 2014    | Amended the week 2 follow-up to allow for flexibility. Expanded 30 month vital status determination to include transplant status.   |
| 26 February 2015 | Added clarification for Hepatitis and HIV exclusion.  |
| 24 May 2016      | Incorporated the discontinuation of enrollment of subjects with wild-type genotype in order to increase the numbers of subjects with variant genotype. Redefined the baseline groupings for New York Heart Association (NYHA) functional classification that will be used for efficacy analyses, grouping subjects with NYHA Class I and II together to be compared against NYHA Class III. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported