



## Clinical trial results:

### A Multinational Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults With Pulmonary Arterial Hypertension (PAH)

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2013-004362-34                         |
| Trial protocol           | SE AT BE DE ES CZ RO PL GR NL PT HR LV |
| Global end of trial date | 26 February 2021                       |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v2 (current)  |
| This version publication date  | 17 July 2022  |
| First version publication date | 18 April 2022 |
| Version creation reason        |               |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A1481324 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02060487 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Viatrix Specialty LLC   |
| Sponsor organisation address | 3711 Collins Ferry Road, Morgantown, United States, WV 26505  |
| Public contact               | Global Clinical Operations Lead, Meda Pharma GmbH & Co. KG (A Viatrix company), Baerbel.Fingerhut@viatrix.com |
| Scientific contact           | Global Clinical Operations Lead, Meda Pharma GmbH & Co. KG (A Viatrix company), Baerbel.Fingerhut@viatrix.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 16 July 2021     |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 February 2021 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To test for the non-inferiority of sildenafil 80 milligrams (mg) versus 5 mg for mortality; mortality rate with the 80 mg dose was to be no worse than double the mortality rate for the 5 mg dose.

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 Conference on Harmonisation (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                          | 22 September 2014 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                            |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Australia: 7               |
| Country: Number of subjects enrolled | Belgium: 1                 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 13 |
| Country: Number of subjects enrolled | Croatia: 10                |
| Country: Number of subjects enrolled | Czechia: 37                |
| Country: Number of subjects enrolled | Germany: 34                |
| Country: Number of subjects enrolled | Greece: 14                 |
| Country: Number of subjects enrolled | Hong Kong: 3               |
| Country: Number of subjects enrolled | Israel: 1                  |
| Country: Number of subjects enrolled | Latvia: 20                 |
| Country: Number of subjects enrolled | Malaysia: 17               |
| Country: Number of subjects enrolled | Mexico: 9                  |
| Country: Number of subjects enrolled | Poland: 1                  |
| Country: Number of subjects enrolled | Romania: 29                |
| Country: Number of subjects enrolled | Russian Federation: 49     |
| Country: Number of subjects enrolled | Serbia: 14                 |
| Country: Number of subjects enrolled | Singapore: 4               |
| Country: Number of subjects enrolled | South Africa: 3            |
| Country: Number of subjects enrolled | Spain: 4                   |
| Country: Number of subjects enrolled | Thailand: 28               |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Turkey: 9         |
| Country: Number of subjects enrolled | Ukraine: 68       |
| Country: Number of subjects enrolled | United States: 10 |
| Worldwide total number of subjects   | 385               |
| EEA total number of subjects         | 150               |

Notes:

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### **Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 291 |
| From 65 to 84 years                       | 94  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a randomised, double-blind, parallel-group, multinational and multicenter study to assess the effects of oral sildenafil on mortality in adult subjects with pulmonary arterial hypertension (PAH). The study was conducted at 68 active sites in 23 countries.

### Pre-assignment

Screening details:

A total of 445 subjects were screened of which, 47 subjects failed screening and 13 subjects were neither screen failures nor randomised. A total of 385 subjects were actually enrolled into the study and assigned to a study treatment.

### 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          |

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Sildenafil 5 mg |

Arm description:

Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Sildenafil citrate |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 5 mg orally thrice daily (TID).

|  |                        |
|--|------------------------|
| Investigational medicinal product name | 80 mg matching placebo |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 80 mg orally TID.

|  |                        |
|--|------------------------|
| Investigational medicinal product name | 20 mg matching placebo |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 20 mg orally TID.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Sildenafil 20 mg |
|------------------|------------------|

Arm description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo

matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Sildenafil citrate |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 20 mg orally TID

|  |                        |
|--|------------------------|
| Investigational medicinal product name | 80 mg matching placebo |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 80 mg orally TID

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | 5 mg matching placebo |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Tablet                |
| Routes of administration               | Oral use              |

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

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

Arm description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | 5 mg matching placebo |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Tablet                |
| Routes of administration               | Oral use              |

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

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

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 80 mg orally TID

|  |                        |
|--|------------------------|
| Investigational medicinal product name | 20 mg matching placebo |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

---

**Dosage and administration details:**

Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

| <b>Number of subjects in period 1</b> | Sildenafil 5 mg | Sildenafil 20 mg | Sildenafil 80 mg |
|---------------------------------------|-----------------|------------------|------------------|
| Started                               | 129             | 128              | 128              |
| Completed                             | 0               | 0                | 0                |
| Not completed                         | 129             | 128              | 128              |
| Consent withdrawn by subject          | 3               | 10               | 4                |
| Study Terminated By Sponsor           | 87              | 89               | 100              |
| Adverse event, non-fatal              | -               | -                | 1                |
| Death                                 | 34              | 25               | 19               |
| Unspecified                           | 1               | 2                | 1                |
| Lost to follow-up                     | 3               | -                | 2                |
| Randomised in error                   | 1               | -                | -                |
| Lack of efficacy                      | -               | 1                | -                |
| Protocol deviation                    | -               | 1                | 1                |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Sildenafil 5 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 20 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 80 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

| Reporting group values                             | Sildenafil 5 mg | Sildenafil 20 mg | Sildenafil 80 mg |
|--|-----------------|------------------|------------------|
| Number of subjects                                 | 129             | 128              | 128              |
| Age categorical                                    |                 |                  |                  |
| Units: Subjects                                    |                 |                  |                  |
| In utero   | 0               | 0                | 0                |
| Preterm newborn infants (gestational age < 37 wks) | 0               | 0                | 0                |
| Newborns (0-27 days)                               | 0               | 0                | 0                |
| Infants and toddlers (28 days-23 months)           | 0               | 0                | 0                |
| Children (2-11 years)                              | 0               | 0                | 0                |
| Adolescents (12-17 years)                          | 0               | 0                | 0                |
| Adults (18-64 years)                               | 98              | 98               | 95               |
| From 65-84 years                                   | 31              | 30               | 33               |
| 85 years and over                                  | 0               | 0                | 0                |
| Age Continuous                                     |                 |                  |                  |
| Units: Years                                       |                 |                  |                  |
| arithmetic mean                                    | 51.4            | 51.2             | 52.1             |
| standard deviation                                 | ± 15.02         | ± 15.81          | ± 14.72          |
| Sex: Female, Male                                  |                 |                  |                  |
| Units: Subjects                                    |                 |                  |                  |
| Female   | 97              | 102              | 98               |
| Male   | 32              | 26               | 30               |
| Race   |                 |                  |                  |
| Units: Subjects                                    |                 |                  |                  |
| Asian  | 23              | 14               | 19               |
| White  | 104             | 113              | 108              |
| Unknown or Not Reported                            | 2               | 1                | 1                |
| Ethnicity  |                 |                  |                  |

|                        |     |     |     |
|------------------------|-----|-----|-----|
| Units: Subjects        |     |     |     |
| Hispanic or Latino     | 5   | 4   | 3   |
| Not Hispanic or Latino | 124 | 124 | 125 |

| <b>Reporting group values</b>                         | Total |  |  |
|---|-------|--|--|
| Number of subjects                                    | 385   |  |  |
| Age categorical                                       |       |  |  |
| Units: Subjects                                       |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 291   |  |  |
| From 65-84 years                                      | 94    |  |  |
| 85 years and over                                     | 0     |  |  |
| Age Continuous  |       |  |  |
| Units: Years  |       |  |  |
| arithmetic mean                                       |       |  |  |
| standard deviation                                    | -     |  |  |
| Sex: Female, Male                                     |       |  |  |
| Units: Subjects                                       |       |  |  |
| Female  | 297   |  |  |
| Male  | 88    |  |  |
| Race  |       |  |  |
| Units: Subjects                                       |       |  |  |
| Asian   | 56    |  |  |
| White   | 325   |  |  |
| Unknown or Not Reported                               | 4     |  |  |
| Ethnicity   |       |  |  |
| Units: Subjects                                       |       |  |  |
| Hispanic or Latino                                    | 12    |  |  |
| Not Hispanic or Latino                                | 373   |  |  |

## End points

### End points reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Sildenafil 5 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 20 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 80 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

### Primary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

In this end point number of deaths during the study were reported. The intent-to-treat population (ITT) included all randomised subjects treated with study treatment.

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

End point timeframe:

Day 1 of study treatment up to date of death (within a maximum duration of 2102 days)

| End point values            | Sildenafil 5 mg | Sildenafil 20 mg | Sildenafil 80 mg |  |
|-----------------------------|-----------------|------------------|------------------|--|
| Subject group type          | Reporting group | Reporting group  | Reporting group  |  |
| Number of subjects analysed | 129             | 128              | 128              |  |
| Units: Subjects             | 34              | 25               | 19               |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Sildenafil 20 mg versus Sildenafil 5 mg TID |
|----------------------------|---|

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

|                   |                                    |
|-------------------|------------------------------------|
| Comparison groups | Sildenafil 5 mg v Sildenafil 20 mg |
|-------------------|------------------------------------|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 257                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.68                           |
| Confidence interval                     |                                |
| level                                   | Other: 99.7 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | 0.31                           |
| upper limit                             | 1.49                           |

Notes:

[1] - Non-inferiority of sildenafil 20 mg TID versus sildenafil 5 mg TID was to be concluded if the upper limit of the 99.7% confidence interval (CI) for hazard ratio (HR) was less than 2.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Sildenafil 80 mg versus Sildenafil 5 mg TID |
|-----------------------------------|---|

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | Sildenafil 5 mg v Sildenafil 80 mg |
| Number of subjects included in analysis | 257                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[2]</sup>     |
| Parameter estimate                      | Hazard ratio (HR)                  |
| Point estimate                          | 0.51                               |
| Confidence interval                     |                                    |
| level                                   | Other: 99.7 %                      |
| sides                                   | 2-sided                            |
| lower limit                             | 0.22                               |
| upper limit                             | 1.21                               |

Notes:

[2] - Non-inferiority of sildenafil 80 mg TID vs. sildenafil 5 mg TID was to be concluded if the upper limit of the 99.7% CI for HR was less than 2.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sildenafil 80 mg versus Sildenafil 20 mg TID |
|-----------------------------------|--|

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Sildenafil 20 mg v Sildenafil 80 mg |
| Number of subjects included in analysis | 256                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | non-inferiority <sup>[3]</sup>      |
| Parameter estimate                      | Hazard ratio (HR)                   |
| Point estimate                          | 0.74                                |
| Confidence interval                     |                                     |
| level                                   | Other: 99.7 %                       |
| sides                                   | 2-sided                             |
| lower limit                             | 0.3                                 |
| upper limit                             | 1.84                                |

Notes:

[3] - Non-inferiority of sildenafil 80 mg TID vs. sildenafil 20 mg TID was to be concluded if the upper limit of the 99.7% CI for HR is less than 2.

## Secondary: Number of Subjects With Clinical Worsening Events

|  |   |
|--|---|
| End point title  | Number of Subjects With Clinical Worsening Events |
| End point description:<br>Clinical worsening was defined as all-cause mortality, non-elective hospital stay for worsening pulmonary arterial hypertension (PAH) (including but not limited to right heart failure [RHF], initiation of intravenous (IV) prostanoids, lung transplantation, or septostomy) or disease progression. Disease progression was defined as a reduction from baseline in the 6-Minute Walk Distance (6MWD) test by 15% and worsening functional class from baseline, both confirmed by second test within 2 weeks of study treatment. ITT population included all randomised subjects treated with study treatment. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Day 1 of study treatment up to date of clinical worsening event (within a maximum duration of 2080 days)   |   |

| End point values            | Sildenafil 5 mg | Sildenafil 20 mg | Sildenafil 80 mg |  |
|-----------------------------|-----------------|------------------|------------------|--|
| Subject group type          | Reporting group | Reporting group  | Reporting group  |  |
| Number of subjects analysed | 129             | 128              | 128              |  |
| Units: Subjects             | 52              | 36               | 28               |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Sildenafil 20 mg versus Sildenafil 5 mg TID |
| Statistical analysis description:<br>Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH. |   |
| Comparison groups   | Sildenafil 5 mg v Sildenafil 20 mg          |
| Number of subjects included in analysis   | 257   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | superiority                                 |
| P-value   | = 0.035                                     |
| Method  | Wald test                                   |
| Parameter estimate  | Hazard ratio (HR)                           |
| Point estimate  | 0.63  |
| Confidence interval   |   |
| level   | Other: 99.7 %                               |
| sides   | 2-sided                                     |
| lower limit   | 0.33  |
| upper limit   | 1.21  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Sildenafil 80 mg versus Sildenafil 5 mg TID |
| Statistical analysis description:<br>Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH. |   |
| Comparison groups   | Sildenafil 5 mg v Sildenafil 80 mg          |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 257               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | < 0.001           |
| Method                                  | Wald test         |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.44              |
| Confidence interval                     |                   |
| level                                   | Other: 99.7 %     |
| sides                                   | 2-sided           |
| lower limit                             | 0.22              |
| upper limit                             | 0.89              |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sildenafil 80 mg versus Sildenafil 20 mg TID |
|-----------------------------------|--|

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Sildenafil 20 mg v Sildenafil 80 mg |
| Number of subjects included in analysis | 256                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.195                             |
| Method                                  | Wald test                           |
| Parameter estimate                      | Hazard ratio (HR)                   |
| Point estimate                          | 0.72                                |
| Confidence interval                     |                                     |
| level                                   | Other: 99.7 %                       |
| sides                                   | 2-sided                             |
| lower limit                             | 0.34                                |
| upper limit                             | 1.52                                |

### **Secondary: Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 6**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 6 |
|-----------------|--|

End point description:

6MWD was the 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. Analysis was performed using mixed model for repeated measures (MMRM), adjusted for baseline 6MWD and for randomisation stratification factors: PAH treatment at study entry and etiology of PAH. ITT population included all randomised subjects treated with study treatment. Here, "overall number of subjects analysed" signifies number of subjects who were evaluable for this outcome measure.

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

End point timeframe:

Baseline, Month 6

| <b>End point values</b>                      | Sildenafil 5 mg       | Sildenafil 20 mg      | Sildenafil 80 mg      |  |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type                           | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed                  | 113                   | 118                   | 116                   |  |
| Units: Meters                                |                       |                       |                       |  |
| least squares mean (confidence interval 95%) | 12.2 (-0.67 to 25.16) | 27.3 (14.52 to 39.99) | 31.2 (18.68 to 43.66) |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Sildenafil 20 mg versus Sildenafil 5 mg TID |
|---|---|
| Comparison groups                       | Sildenafil 5 mg v Sildenafil 20 mg          |
| Number of subjects included in analysis | 231   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.0627                                    |
| Method                                  | MMRM  |
| Parameter estimate                      | Least-squares means difference              |
| Point estimate                          | 15  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | -0.8  |
| upper limit                             | 30.81                                       |

| <b>Statistical analysis title</b>       | Sildenafil 80 mg versus Sildenafil 20 mg TID |
|---|--|
| Comparison groups                       | Sildenafil 20 mg v Sildenafil 80 mg          |
| Number of subjects included in analysis | 234  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.6254                                     |
| Method                                  | MMRM   |
| Parameter estimate                      | Least-squares means difference               |
| Point estimate                          | 3.9  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -11.85                                       |
| upper limit                             | 19.68  |

| <b>Statistical analysis title</b> | Sildenafil 80 mg versus Sildenafil 5 mg TID |
|-----------------------------------|---|
| Comparison groups                 | Sildenafil 5 mg v Sildenafil 80 mg          |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 229                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0201                       |
| Method                                  | MMRM                           |
| Parameter estimate                      | Least-squares means difference |
| Point estimate                          | 18.9                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.99                           |
| upper limit                             | 34.86                          |

### Secondary: Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 12 |
|-----------------|---|

End point description:

6MWD was the distance that a subject could walk in 6 minutes. Participants were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Analysis was performed using mixed model for repeated measures (MMRM), adjusted for baseline 6MWD and for randomization stratification factors: PAH treatment at study entry and etiology of PAH. ITT population included all randomised subjects treated with study treatment. Here, "overall number of subjects analysed" signifies number of subjects who were evaluable for this outcome measure.

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

End point timeframe:

Baseline, Month 12

| End point values                             | Sildenafil 5 mg       | Sildenafil 20 mg      | Sildenafil 80 mg      |  |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type                           | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed                  | 88                    | 89                    | 89                    |  |
| Units: Meters                                |                       |                       |                       |  |
| least squares mean (confidence interval 95%) | 14.3 (-0.58 to 29.27) | 35.7 (20.91 to 50.48) | 34.8 (20.21 to 49.43) |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Sildenafil 20 mg versus Sildenafil 5 mg TID |
| Comparison groups                       | Sildenafil 5 mg v Sildenafil 20 mg          |
| Number of subjects included in analysis | 177   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.0286                                    |
| Method                                  | MMRM  |
| Parameter estimate                      | Least-squares means difference              |
| Point estimate                          | 21.3  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 2.25    |
| upper limit         | 40.45   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Sildenafil 80 mg versus Sildenafil 5 mg TID |
| Comparison groups                       | Sildenafil 5 mg v Sildenafil 80 mg          |
| Number of subjects included in analysis | 177   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | superiority                                 |
| P-value                                 | = 0.0364                                    |
| Method                                  | MMRM  |
| Parameter estimate                      | Least-squares means difference              |
| Point estimate                          | 20.5  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 1.3   |
| upper limit                             | 39.65                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Sildenafil 80 mg versus Sildenafil 20 mg TID |
| Comparison groups                       | Sildenafil 20 mg v Sildenafil 80 mg          |
| Number of subjects included in analysis | 178  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.9283                                     |
| Method                                  | MMRM   |
| Parameter estimate                      | Least-squares means difference               |
| Point estimate                          | -0.9   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -19.94                                       |
| upper limit                             | 18.19  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study treatment (up to a maximum duration of 2108 days for sildenafil 5 mg; up to a maximum duration of 2012 days for sildenafil 20 mg; up to a maximum duration of 2101 days for sildenafil 80 mg)

Adverse event reporting additional description:

An AE term may be reported as both a serious and non-serious AE, but are distinct events. An AE may be serious for 1 subject and non-serious for another subject, or a subject may have experienced both a serious and non-serious episode of the same event. Safety population comprised of all randomised subjects treated with study treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Sildenafil 5 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 5 mg along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 20 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Sildenafil 80 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

| <b>Serious adverse events</b>                                       | Sildenafil 5 mg   | Sildenafil 20 mg  | Sildenafil 80 mg  |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed   | 66 / 129 (51.16%) | 49 / 128 (38.28%) | 51 / 128 (39.84%) |
| number of deaths (all causes)                                       | 34                | 25                | 19                |
| number of deaths resulting from adverse events                      |                   |                   |                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Cervix carcinoma  |                   |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 1 / 128 (0.78%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0             |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal carcinoma                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Hepatocellular carcinoma                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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 neoplasm                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myelofibrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleomorphic malignant fibrous histiocytoma      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural neoplasm                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal adenocarcinoma                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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 stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Peripheral arterial occlusive disease           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Shock   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Varicose ulceration                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                 |                 |                 |                 |
| Drug therapy                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Hospitalisation                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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 transplant                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>General disorders and administration site conditions</b> |                 |                 |                 |
| <b>Chest pain</b>   |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all             | 0 / 0           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Condition aggravated</b>                                 |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Death</b>  |                 |                 |                 |
| subjects affected / exposed                                 | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all             | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 2           | 0 / 0           | 0 / 1           |
| <b>Disease progression</b>                                  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| <b>Exercise tolerance decreased</b>                         |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>General physical health deterioration</b>                |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Multiple organ dysfunction syndrome</b>                  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Oedema</b>   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Peripheral swelling                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Sudden cardiac death                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Sudden death                                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0           | 0 / 0           |
| Vascular stent stenosis                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Drug hypersensitivity                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Ovarian cyst ruptured                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Alveolitis</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Asthma</b>                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Chronic obstructive pulmonary disease</b>    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 27          | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Chronic respiratory failure</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Dyspnoea</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 1 / 128 (0.78%) | 4 / 128 (3.13%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 1           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Epistaxis</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Hyperventilation</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Hypoxia</b>                                  |                 |                 |                 |

|   |                   |                  |                 |
|---|-------------------|------------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%)   | 2 / 128 (1.56%)  | 0 / 128 (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           |
| <b>Interstitial lung disease</b>                |                   |                  |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)   | 1 / 128 (0.78%)  | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Pleural effusion</b>                         |                   |                  |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Pneumothorax spontaneous</b>                 |                   |                  |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Pulmonary arterial hypertension</b>          |                   |                  |                 |
| subjects affected / exposed                     | 17 / 129 (13.18%) | 10 / 128 (7.81%) | 8 / 128 (6.25%) |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 16           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Pulmonary embolism</b>                       |                   |                  |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)   | 2 / 128 (1.56%)  | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Pulmonary fibrosis</b>                       |                   |                  |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)   | 0 / 128 (0.00%)  | 0 / 128 (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           |
| <b>Pulmonary hypertension</b>                   |                   |                  |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%)   | 4 / 128 (3.13%)  | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5            | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0           |
| <b>Respiratory disorder</b>                     |                   |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Respiratory failure</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Systemic sclerosis pulmonary</b>             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Tachypnoea</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Vocal cord dysfunction</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Psychiatric disorders</b>                    |                 |                 |                 |
| <b>Delusion</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Product issues</b>                           |                 |                 |                 |
| <b>Device dislocation</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Investigations</b>                           |                 |                 |                 |
| <b>Haemodynamic test</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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, poisoning and procedural complications  |                 |                 |                 |
| Clavicle fracture                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Procedural intestinal perforation               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin laceration                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thermal burn                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Thoracic vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (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           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradyarrhythmia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 3 / 128 (2.34%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 9 / 129 (6.98%) | 8 / 128 (6.25%) | 3 / 128 (2.34%) |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 9           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Cardiac failure acute                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 3 / 128 (2.34%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 6           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiovascular insufficiency                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (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           |
| Left ventricular failure                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Pericardial effusion                            |                 |                 |                 |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 0 / 128 (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           |
| Right ventricular failure                       |                  |                 |                 |
| subjects affected / exposed                     | 11 / 129 (8.53%) | 4 / 128 (3.13%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 16           | 0 / 4           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Supraventricular extrasystoles                  |                  |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 0 / 128 (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 paroxysmal                          |                  |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (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           |
| Nervous system disorders                        |                  |                 |                 |
| Ataxia  |                  |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 0 / 128 (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           |
| Cerebrovascular accident                        |                  |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)  | 2 / 128 (1.56%) | 0 / 128 (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           |
| Dizziness                                       |                  |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (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           |
| Guillain-Barre syndrome                         |                  |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 0 / 128 (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           |
| Migraine  |                  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Presyncope</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Sciatica</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Syncope</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Transient ischaemic attack</b>               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| <b>Anaemia</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood loss anaemia</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypochromic anaemia</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Thrombosis mesenteric vessel                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Umbilical hernia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Portal vein thrombosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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 and subcutaneous tissue disorders          |                 |                 |                 |
| Hypersensitivity vasculitis                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vasculitic rash                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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                     | 4 / 129 (3.10%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Connective tissue disorder                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Oligoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Osteoporotic fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Rheumatic disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Rheumatoid arthritis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Rotator cuff syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Scleroderma                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 3 / 128 (2.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 3 / 128 (2.34%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Cystitis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Dengue fever                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Diarrhoea infectious                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Encephalitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocarditis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (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           |
| Escherichia urinary tract infection             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Gangrene  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis viral                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Gastrointestinal infection</b>               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>H1N1 influenza</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infectious pleural effusion</b>              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Influenza</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| <b>Klebsiella bacteraemia</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Leptospirosis</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Lower respiratory tract infection</b>        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Lung abscess</b>                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Osteomyelitis chronic</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Parainfluenzae virus infection</b>           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Pharyngitis</b>                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Pneumonia</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 7 / 129 (5.43%) | 6 / 128 (4.69%) | 3 / 128 (2.34%) |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 6           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Pneumonia influenzal</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| <b>Postoperative wound infection</b>            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Respiratory tract infection</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Sepsis</b>                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal infection                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Streptococcal bacteraemia                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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 respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral upper respiratory tract infection         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| 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                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Fluid overload                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (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           |
| Hypovolaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |
| Metabolic acidosis                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (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           |

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

| <b>Non-serious adverse events</b>                                   | Sildenafil 5 mg    | Sildenafil 20 mg   | Sildenafil 80 mg   |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events               |                    |                    |                    |
| subjects affected / exposed   | 108 / 129 (83.72%) | 107 / 128 (83.59%) | 111 / 128 (86.72%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                    |
| B-cell lymphoma stage IV  |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 0                  | 0                  | 1                  |
| Basal cell carcinoma  |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 0                  | 0                  | 1                  |
| Benign pancreatic neoplasm  |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 1 / 128 (0.78%)    | 0 / 128 (0.00%)    |
| occurrences (all)   | 0                  | 1                  | 0                  |
| Bowen's disease   |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 0                  | 0                  | 1                  |
| Breast cancer   |                    |                    |                    |
| subjects affected / exposed   | 1 / 129 (0.78%)    | 0 / 128 (0.00%)    | 0 / 128 (0.00%)    |
| occurrences (all)   | 1                  | 0                  | 0                  |
| Haemangioma of bone   |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 1 / 128 (0.78%)    | 0 / 128 (0.00%)    |
| occurrences (all)   | 0                  | 1                  | 0                  |
| Haemangioma of liver  |                    |                    |                    |
| subjects affected / exposed   | 1 / 129 (0.78%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 1                  | 0                  | 2                  |
| Lipoma  |                    |                    |                    |
| subjects affected / exposed   | 1 / 129 (0.78%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 2                  | 0                  | 1                  |
| Malignant melanoma  |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 1 / 128 (0.78%)    | 0 / 128 (0.00%)    |
| occurrences (all)   | 0                  | 1                  | 0                  |
| Melanocytic naevus  |                    |                    |                    |
| subjects affected / exposed   | 0 / 129 (0.00%)    | 0 / 128 (0.00%)    | 1 / 128 (0.78%)    |
| occurrences (all)   | 0                  | 0                  | 1                  |
| Myelofibrosis   |                    |                    |                    |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Myeloproliferative neoplasm<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Polycythaemia vera<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Rectal neoplasm<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Skin papilloma<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>2 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Uterine leiomyoma<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| <b>Vascular disorders</b>   |                      |                      |                      |
| Aortic stenosis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 129 (0.78%)<br>3 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| Cyanosis<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 129 (0.78%)<br>2 | 1 / 128 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 |
| Deep vein thrombosis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Flushing<br>subjects affected / exposed<br>occurrences (all)                    | 6 / 129 (4.65%)<br>6 | 3 / 128 (2.34%)<br>5 | 4 / 128 (3.13%)<br>4 |
| Haematoma<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>2 |
| Haemorrhage<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Hot flush                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 3 / 128 (2.34%) | 2 / 128 (1.56%) |
| occurrences (all)           | 0               | 3               | 3               |
| Hyperaemia                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hypertension                |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 6 / 128 (4.69%) | 5 / 128 (3.91%) |
| occurrences (all)           | 2               | 9               | 5               |
| Hypertensive crisis         |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 3               | 0               | 0               |
| Hypotension                 |                 |                 |                 |
| subjects affected / exposed | 9 / 129 (6.98%) | 6 / 128 (4.69%) | 7 / 128 (5.47%) |
| occurrences (all)           | 11              | 6               | 15              |
| Jugular vein thrombosis     |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Labile blood pressure       |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Lymphoedema                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Neovascularisation          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Pelvic venous thrombosis    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Peripheral venous disease   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Phlebitis                   |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Raynaud's phenomenon<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Varicose vein<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Vasodilatation<br>subjects affected / exposed<br>occurrences (all)       | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| <b>Surgical and medical procedures</b>                                   |                      |                      |                      |
| Cancer surgery<br>subjects affected / exposed<br>occurrences (all)       | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Cardiac ablation<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Cataract operation<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>2 | 3 / 128 (2.34%)<br>4 |
| Dental operation<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Haematoma evacuation<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Myomectomy<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Tooth extraction<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>2 | 1 / 128 (0.78%)<br>1 |
| Tooth repair   |                      |                      |                      |

|   |                 |                   |                   |
|---|-----------------|-------------------|-------------------|
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 1               | 0                 | 0                 |
| Vascular operation  |                 |                   |                   |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 1               | 0                 | 0                 |
| <b>General disorders and administration site conditions</b> |                 |                   |                   |
| <b>Asthenia</b>   |                 |                   |                   |
| subjects affected / exposed                                 | 3 / 129 (2.33%) | 7 / 128 (5.47%)   | 2 / 128 (1.56%)   |
| occurrences (all)   | 3               | 14                | 3                 |
| <b>Catheter site erythema</b>                               |                 |                   |                   |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)   | 0               | 0                 | 1                 |
| <b>Chest discomfort</b>                                     |                 |                   |                   |
| subjects affected / exposed                                 | 3 / 129 (2.33%) | 3 / 128 (2.34%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 11              | 6                 | 0                 |
| <b>Chest pain</b>   |                 |                   |                   |
| subjects affected / exposed                                 | 7 / 129 (5.43%) | 15 / 128 (11.72%) | 13 / 128 (10.16%) |
| occurrences (all)   | 9               | 30                | 72                |
| <b>Chills</b>   |                 |                   |                   |
| subjects affected / exposed                                 | 2 / 129 (1.55%) | 1 / 128 (0.78%)   | 5 / 128 (3.91%)   |
| occurrences (all)   | 2               | 1                 | 5                 |
| <b>Crying</b>   |                 |                   |                   |
| subjects affected / exposed                                 | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 1               | 0                 | 0                 |
| <b>Cyst</b>   |                 |                   |                   |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)   | 0               | 0                 | 3                 |
| <b>Disease progression</b>                                  |                 |                   |                   |
| subjects affected / exposed                                 | 3 / 129 (2.33%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 3               | 0                 | 0                 |
| <b>Face oedema</b>  |                 |                   |                   |
| subjects affected / exposed                                 | 0 / 129 (0.00%) | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)   | 0               | 2                 | 0                 |
| <b>Facial pain</b>  |                 |                   |                   |

|                                       |                  |                  |                 |
|---------------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed           | 0 / 129 (0.00%)  | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)                     | 0                | 0                | 1               |
| Fatigue                               |                  |                  |                 |
| subjects affected / exposed           | 11 / 129 (8.53%) | 10 / 128 (7.81%) | 9 / 128 (7.03%) |
| occurrences (all)                     | 19               | 17               | 18              |
| Feeling cold                          |                  |                  |                 |
| subjects affected / exposed           | 2 / 129 (1.55%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 4                | 1                | 0               |
| Feeling hot                           |                  |                  |                 |
| subjects affected / exposed           | 1 / 129 (0.78%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 16               | 2                | 0               |
| Gait disturbance                      |                  |                  |                 |
| subjects affected / exposed           | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 1                | 0                | 0               |
| General physical health deterioration |                  |                  |                 |
| subjects affected / exposed           | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 1                | 0                | 0               |
| Generalised oedema                    |                  |                  |                 |
| subjects affected / exposed           | 1 / 129 (0.78%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 1                | 1                | 0               |
| Ill-defined disorder                  |                  |                  |                 |
| subjects affected / exposed           | 0 / 129 (0.00%)  | 2 / 128 (1.56%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 0                | 2                | 0               |
| Inflammation                          |                  |                  |                 |
| subjects affected / exposed           | 0 / 129 (0.00%)  | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)                     | 0                | 0                | 1               |
| Influenza like illness                |                  |                  |                 |
| subjects affected / exposed           | 0 / 129 (0.00%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 0                | 1                | 0               |
| Infusion site pain                    |                  |                  |                 |
| subjects affected / exposed           | 0 / 129 (0.00%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 0                | 1                | 0               |
| Injection site hypersensitivity       |                  |                  |                 |
| subjects affected / exposed           | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)                     | 1                | 0                | 0               |
| Malaise                               |                  |                  |                 |

|                                |                   |                   |                 |
|--------------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed    | 0 / 129 (0.00%)   | 2 / 128 (1.56%)   | 1 / 128 (0.78%) |
| occurrences (all)              | 0                 | 3                 | 1               |
| Mucosal dryness                |                   |                   |                 |
| subjects affected / exposed    | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 1                 | 0                 | 0               |
| Oedema                         |                   |                   |                 |
| subjects affected / exposed    | 3 / 129 (2.33%)   | 2 / 128 (1.56%)   | 3 / 128 (2.34%) |
| occurrences (all)              | 5                 | 2                 | 4               |
| Oedema peripheral              |                   |                   |                 |
| subjects affected / exposed    | 14 / 129 (10.85%) | 17 / 128 (13.28%) | 8 / 128 (6.25%) |
| occurrences (all)              | 18                | 25                | 9               |
| Pain                           |                   |                   |                 |
| subjects affected / exposed    | 2 / 129 (1.55%)   | 1 / 128 (0.78%)   | 3 / 128 (2.34%) |
| occurrences (all)              | 3                 | 3                 | 3               |
| Peripheral swelling            |                   |                   |                 |
| subjects affected / exposed    | 7 / 129 (5.43%)   | 6 / 128 (4.69%)   | 5 / 128 (3.91%) |
| occurrences (all)              | 9                 | 6                 | 7               |
| Pyrexia                        |                   |                   |                 |
| subjects affected / exposed    | 3 / 129 (2.33%)   | 9 / 128 (7.03%)   | 9 / 128 (7.03%) |
| occurrences (all)              | 3                 | 11                | 15              |
| Swelling                       |                   |                   |                 |
| subjects affected / exposed    | 2 / 129 (1.55%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 2                 | 0                 | 0               |
| Swelling face                  |                   |                   |                 |
| subjects affected / exposed    | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 0                 | 1                 | 0               |
| Ulcer                          |                   |                   |                 |
| subjects affected / exposed    | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 0                 | 1                 | 0               |
| Vessel puncture site bruise    |                   |                   |                 |
| subjects affected / exposed    | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 1                 | 0                 | 0               |
| Vessel puncture site haematoma |                   |                   |                 |
| subjects affected / exposed    | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)              | 1                 | 0                 | 0               |
| Immune system disorders        |                   |                   |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Allergy to arthropod bite<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| Food allergy<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)           | 2 / 129 (1.55%)<br>3 | 2 / 128 (1.56%)<br>2 | 1 / 128 (0.78%)<br>1 |
| Multiple allergies<br>subjects affected / exposed<br>occurrences (all)         | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| Secondary immunodeficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Reproductive system and breast disorders                                       |                      |                      |                      |
| Amenorrhoea<br>subjects affected / exposed<br>occurrences (all)                | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Breast cyst<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>2 |
| Breast inflammation<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Breast mass<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Breast pain  |                      |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                   | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Dysfunctional uterine bleeding<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>6 | 1 / 128 (0.78%)<br>1 |
| Endometriosis<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Gynaecomastia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Menorrhagia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 129 (1.55%)<br>2 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Menstrual disorder<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Ovarian cyst<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Priapism<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 129 (0.78%)<br>2 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Uterine polyp<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>3 | 1 / 128 (0.78%)<br>1 |
| Vulvovaginal pruritus<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Respiratory, thoracic and mediastinal  |                      |                      |                      |

|                                       |                   |                   |                  |
|---------------------------------------|-------------------|-------------------|------------------|
| disorders                             |                   |                   |                  |
| Alveolitis                            |                   |                   |                  |
| subjects affected / exposed           | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)  |
| occurrences (all)                     | 1                 | 0                 | 0                |
| Asthma                                |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 2 / 128 (1.56%)  |
| occurrences (all)                     | 0                 | 1                 | 3                |
| Bronchial hyperreactivity             |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)  |
| occurrences (all)                     | 0                 | 0                 | 1                |
| Bronchitis chronic                    |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 2 / 128 (1.56%)  |
| occurrences (all)                     | 0                 | 1                 | 2                |
| Bronchopneumopathy                    |                   |                   |                  |
| subjects affected / exposed           | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)  |
| occurrences (all)                     | 1                 | 0                 | 0                |
| Catarrh                               |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)  |
| occurrences (all)                     | 0                 | 0                 | 1                |
| Chronic obstructive pulmonary disease |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 2 / 128 (1.56%)  |
| occurrences (all)                     | 0                 | 1                 | 4                |
| Chronic respiratory failure           |                   |                   |                  |
| subjects affected / exposed           | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 1 / 128 (0.78%)  |
| occurrences (all)                     | 0                 | 1                 | 1                |
| Cough                                 |                   |                   |                  |
| subjects affected / exposed           | 14 / 129 (10.85%) | 11 / 128 (8.59%)  | 12 / 128 (9.38%) |
| occurrences (all)                     | 24                | 14                | 25               |
| Dysphonia                             |                   |                   |                  |
| subjects affected / exposed           | 2 / 129 (1.55%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)  |
| occurrences (all)                     | 3                 | 1                 | 0                |
| Dyspnoea                              |                   |                   |                  |
| subjects affected / exposed           | 12 / 129 (9.30%)  | 16 / 128 (12.50%) | 11 / 128 (8.59%) |
| occurrences (all)                     | 15                | 35                | 16               |
| Dyspnoea exertional                   |                   |                   |                  |

|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed             | 1 / 129 (0.78%)  | 3 / 128 (2.34%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                | 4                 | 0                 |
| <b>Emphysema</b>                        |                  |                   |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                | 0                 | 0                 |
| <b>Epistaxis</b>                        |                  |                   |                   |
| subjects affected / exposed             | 11 / 129 (8.53%) | 13 / 128 (10.16%) | 13 / 128 (10.16%) |
| occurrences (all)                       | 12               | 21                | 22                |
| <b>Haemoptysis</b>                      |                  |                   |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)  | 3 / 128 (2.34%)   | 1 / 128 (0.78%)   |
| occurrences (all)                       | 2                | 3                 | 1                 |
| <b>Hiccups</b>                          |                  |                   |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                | 0                 | 0                 |
| <b>Hyperventilation</b>                 |                  |                   |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| <b>Hypoxia</b>                          |                  |                   |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)  | 3 / 128 (2.34%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                | 4                 | 0                 |
| <b>Idiopathic pulmonary fibrosis</b>    |                  |                   |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 2                | 0                 | 0                 |
| <b>Increased upper airway secretion</b> |                  |                   |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| <b>Interstitial lung disease</b>        |                  |                   |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                | 1                 | 0                 |
| <b>Lung disorder</b>                    |                  |                   |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| <b>Lung infiltration</b>                |                  |                   |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                | 1                 | 0                 |
| <b>Nasal congestion</b>                 |                  |                   |                   |

|                                 |                  |                 |                 |
|---------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed     | 8 / 129 (6.20%)  | 4 / 128 (3.13%) | 5 / 128 (3.91%) |
| occurrences (all)               | 10               | 6               | 5               |
| Nasal dryness                   |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)               | 0                | 1               | 0               |
| Oropharyngeal pain              |                  |                 |                 |
| subjects affected / exposed     | 2 / 129 (1.55%)  | 6 / 128 (4.69%) | 2 / 128 (1.56%) |
| occurrences (all)               | 2                | 11              | 3               |
| Paranasal sinus discomfort      |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)               | 0                | 0               | 1               |
| Pharyngeal swelling             |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)               | 0                | 1               | 0               |
| Pleural effusion                |                  |                 |                 |
| subjects affected / exposed     | 2 / 129 (1.55%)  | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)               | 2                | 0               | 0               |
| Pleurisy                        |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)               | 0                | 2               | 0               |
| Pleuritic pain                  |                  |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)               | 1                | 0               | 0               |
| Productive cough                |                  |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%)  | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)               | 1                | 2               | 1               |
| Prolonged expiration            |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)               | 0                | 1               | 0               |
| Pulmonary arterial hypertension |                  |                 |                 |
| subjects affected / exposed     | 10 / 129 (7.75%) | 7 / 128 (5.47%) | 4 / 128 (3.13%) |
| occurrences (all)               | 15               | 8               | 7               |
| Pulmonary embolism              |                  |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)               | 0                | 1               | 0               |
| Pulmonary fibrosis              |                  |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Pulmonary hypertension      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 1               | 1               |
| Pulmonary vascular disorder |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Rales                       |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Respiratory disorder        |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 4               | 0               | 0               |
| Respiratory failure         |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 2               | 1               | 1               |
| Rhinitis allergic           |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 2               | 0               |
| Rhinorrhoea                 |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 4 / 128 (3.13%) | 3 / 128 (2.34%) |
| occurrences (all)           | 2               | 5               | 3               |
| Rhonchi                     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Sinonasal obstruction       |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Sinus congestion            |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Sleep apnoea syndrome       |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences (all)           | 0               | 0               | 2               |
| Sneezing                    |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Throat irritation           |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Upper-airway cough syndrome |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)           | 0               | 1               | 3               |
| Vasomotor rhinitis          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Vocal cord polyp            |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Wheezing                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Psychiatric disorders       |                 |                 |                 |
| Anxiety                     |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)           | 3               | 2               | 1               |
| Apathy                      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Confusional state           |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Depressed mood              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Depression                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 3 / 128 (2.34%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 3               | 1               |
| Emotional disorder          |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Initial insomnia            |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Insomnia                    |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 5 / 128 (3.91%) | 2 / 128 (1.56%) |
| occurrences (all)           | 27              | 6               | 2               |
| Mental disorder             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Mood altered                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Mood swings                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Nervousness                 |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Sleep disorder              |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 3 / 128 (2.34%) | 1 / 128 (0.78%) |
| occurrences (all)           | 5               | 3               | 1               |
| Product issues              |                 |                 |                 |
| Device breakage             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Device fastener issue       |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hepatobiliary disorders     |                 |                 |                 |
| Biliary dilatation          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Biliary dyskinesia          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Cardiac cirrhosis           |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Cholecystitis               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Cholecystocholangitis       |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Cholelithiasis              |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)           | 4               | 3               | 1               |
| Congestive hepatopathy      |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Hepatic cirrhosis           |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hepatic function abnormal   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hepatic steatosis           |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Hepatitis                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hepatomegaly                |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 0               | 2               |
| Hepatosplenomegaly          |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hyperbilirubinaemia         |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 4 / 128 (3.13%) | 0 / 128 (0.00%) |
| occurrences (all)           | 3               | 4               | 0               |
| Liver disorder              |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Ocular icterus<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| <b>Investigations</b>   |                      |                      |                      |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>1 | 2 / 128 (1.56%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Blood albumin abnormal<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)               | 3 / 129 (2.33%)<br>7 | 3 / 128 (2.34%)<br>3 | 3 / 128 (2.34%)<br>3 |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 |
| Blood glucose decreased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Blood iron decreased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Blood potassium abnormal  |                      |                      |                      |

|                                    |                 |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Blood pressure decreased           |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                  | 0               | 4               | 2               |
| Blood pressure diastolic decreased |                 |                 |                 |
| subjects affected / exposed        | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                  | 2               | 1               | 1               |
| Blood pressure increased           |                 |                 |                 |
| subjects affected / exposed        | 3 / 129 (2.33%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                  | 12              | 1               | 2               |
| Blood pressure measurement         |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Blood urea increased               |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                  | 1               | 1               | 1               |
| Blood uric acid increased          |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 2 / 128 (1.56%) |
| occurrences (all)                  | 0               | 2               | 2               |
| Body temperature increased         |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)                  | 0               | 9               | 1               |
| Breath sounds abnormal             |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Colonoscopy                        |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Endoscopy                          |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                  | 0               | 0               | 1               |
| Fibrin D dimer increased           |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Haemodynamic test                  |                 |                 |                 |

|                              |                 |                 |                 |
|------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed  | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)            | 0               | 2               | 0               |
| Heart rate                   |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)            | 0               | 1               | 0               |
| Heart rate decreased         |                 |                 |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)            | 1               | 0               | 1               |
| Heart rate increased         |                 |                 |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 1               | 0               |
| Heart sounds abnormal        |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)            | 0               | 1               | 0               |
| Liver function test abnormal |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0               | 1               |
| Oxygen saturation decreased  |                 |                 |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |
| Platelet count decreased     |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0               | 1               |
| Protein total abnormal       |                 |                 |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |
| SARS-CoV-2 test positive     |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 1               | 1               |
| Staphylococcus test positive |                 |                 |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)            | 0               | 1               | 0               |
| Transaminases increased      |                 |                 |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 1               | 0               |
| Troponin increased           |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                    | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                              | 1               | 0               | 0               |
| Ultrasound scan                                |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                              | 0               | 0               | 1               |
| Venous pressure jugular increased              |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                              | 0               | 2               | 0               |
| Vitamin D decreased                            |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                              | 0               | 0               | 1               |
| Walking distance test abnormal                 |                 |                 |                 |
| subjects affected / exposed                    | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                              | 3               | 0               | 0               |
| Weight decreased                               |                 |                 |                 |
| subjects affected / exposed                    | 4 / 129 (3.10%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                              | 7               | 1               | 2               |
| Weight increased                               |                 |                 |                 |
| subjects affected / exposed                    | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                              | 2               | 1               | 1               |
| White blood cell count increased               |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                              | 0               | 1               | 2               |
| Injury, poisoning and procedural complications |                 |                 |                 |
| Arthropod bite                                 |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)                              | 0               | 3               | 1               |
| Arthropod sting                                |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                              | 0               | 1               | 0               |
| Back injury                                    |                 |                 |                 |
| subjects affected / exposed                    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                              | 0               | 2               | 0               |
| Burn oral cavity                               |                 |                 |                 |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Chest injury                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences (all)                    | 0               | 0               | 2               |
| Contusion                            |                 |                 |                 |
| subjects affected / exposed          | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 1               | 2               | 1               |
| Endotracheal intubation complication |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Epicondylitis                        |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Exposure via breast milk             |                 |                 |                 |
| subjects affected / exposed          | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Facial bones fracture                |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Fall                                 |                 |                 |                 |
| subjects affected / exposed          | 4 / 129 (3.10%) | 2 / 128 (1.56%) | 3 / 128 (2.34%) |
| occurrences (all)                    | 4               | 2               | 5               |
| Head injury                          |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 0               | 2               | 1               |
| Humerus fracture                     |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Ligament sprain                      |                 |                 |                 |
| subjects affected / exposed          | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 1               | 0               | 1               |
| Limb injury                          |                 |                 |                 |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Lower limb fracture                  |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Muscle injury               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Muscle rupture              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Muscle strain               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 1               | 2               |
| Nasal injury                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Oral contusion              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Post procedural haemorrhage |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Procedural pain             |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 0               | 1               |
| Rib fracture                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 2               | 1               |
| Road traffic accident       |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Scar                        |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Skin abrasion               |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Skin laceration             |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Soft tissue injury<br>subjects affected / exposed<br>occurrences (all)          | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Thoracic vertebral fracture<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)              | 2 / 129 (1.55%)<br>2 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Upper limb fracture<br>subjects affected / exposed<br>occurrences (all)         | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| <b>Congenital, familial and genetic disorders</b>                               |                      |                      |                      |
| Atrial septal defect<br>subjects affected / exposed<br>occurrences (all)        | 2 / 129 (1.55%)<br>2 | 2 / 128 (1.56%)<br>2 | 1 / 128 (0.78%)<br>1 |
| Thyroid malformation<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| <b>Cardiac disorders</b>  |                      |                      |                      |
| Acute coronary syndrome<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 4 / 128 (3.13%)<br>8 | 2 / 128 (1.56%)<br>3 |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 1 / 128 (0.78%)<br>3 |
| Atrial fibrillation   |                      |                      |                      |

|                                     |                 |                 |                 |
|-------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed         | 2 / 129 (1.55%) | 3 / 128 (2.34%) | 2 / 128 (1.56%) |
| occurrences (all)                   | 2               | 4               | 2               |
| Atrial flutter                      |                 |                 |                 |
| subjects affected / exposed         | 3 / 129 (2.33%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                   | 4               | 1               | 1               |
| Atrial thrombosis                   |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                   | 1               | 0               | 0               |
| Atrioventricular block first degree |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                   | 1               | 0               | 0               |
| Bradycardia                         |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                   | 1               | 0               | 0               |
| Cardiac failure                     |                 |                 |                 |
| subjects affected / exposed         | 3 / 129 (2.33%) | 0 / 128 (0.00%) | 3 / 128 (2.34%) |
| occurrences (all)                   | 3               | 0               | 4               |
| Cardiac failure acute               |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                   | 1               | 0               | 1               |
| Cardiac failure congestive          |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                   | 1               | 2               | 1               |
| Cardiac ventricular thrombosis      |                 |                 |                 |
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                   | 1               | 0               | 0               |
| Coronary artery stenosis            |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                   | 0               | 1               | 0               |
| Extrasystoles                       |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                   | 0               | 0               | 1               |
| Palpitations                        |                 |                 |                 |
| subjects affected / exposed         | 5 / 129 (3.88%) | 5 / 128 (3.91%) | 6 / 128 (4.69%) |
| occurrences (all)                   | 6               | 6               | 19              |
| Pericardial effusion                |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                   | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>3 | 1 / 128 (0.78%)<br>1 |
| Right ventricular dysfunction<br>subjects affected / exposed<br>occurrences (all)  | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Right ventricular failure<br>subjects affected / exposed<br>occurrences (all)      | 3 / 129 (2.33%)<br>3 | 2 / 128 (1.56%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Supraventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all) | 2 / 129 (1.55%)<br>3 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Supraventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 129 (1.55%)<br>3 | 2 / 128 (1.56%)<br>7 | 5 / 128 (3.91%)<br>5 |
| Tricuspid valve incompetence<br>subjects affected / exposed<br>occurrences (all)   | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>2 | 0 / 128 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 |
| Ventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| <b>Nervous system disorders</b>  |                      |                      |                      |
| Ageusia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Anosmia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |

|                               |                  |                   |                   |
|-------------------------------|------------------|-------------------|-------------------|
| <b>Aphasia</b>                |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 2 / 128 (1.56%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 0                | 2                 | 0                 |
| <b>Balance disorder</b>       |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)             | 0                | 0                 | 1                 |
| <b>Burning sensation</b>      |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 128 (0.00%)   | 2 / 128 (1.56%)   |
| occurrences (all)             | 0                | 0                 | 2                 |
| <b>Carpal tunnel syndrome</b> |                  |                   |                   |
| subjects affected / exposed   | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 1                | 0                 | 0                 |
| <b>Cerebral atrophy</b>       |                  |                   |                   |
| subjects affected / exposed   | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 2                | 0                 | 0                 |
| <b>Cervical radiculopathy</b> |                  |                   |                   |
| subjects affected / exposed   | 1 / 129 (0.78%)  | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 1                | 0                 | 0                 |
| <b>Cognitive disorder</b>     |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)             | 0                | 0                 | 1                 |
| <b>Diabetic neuropathy</b>    |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 128 (0.00%)   | 2 / 128 (1.56%)   |
| occurrences (all)             | 0                | 0                 | 2                 |
| <b>Dizziness</b>              |                  |                   |                   |
| subjects affected / exposed   | 12 / 129 (9.30%) | 15 / 128 (11.72%) | 18 / 128 (14.06%) |
| occurrences (all)             | 17               | 21                | 30                |
| <b>Dizziness exertional</b>   |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 2 / 128 (1.56%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 0                | 4                 | 0                 |
| <b>Encephalopathy</b>         |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 0                | 1                 | 0                 |
| <b>Epilepsy</b>               |                  |                   |                   |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)             | 0                | 1                 | 0                 |

|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| Head discomfort             |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 2 / 128 (1.56%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 0                 | 2                 | 0                 |
| Headache                    |                   |                   |                   |
| subjects affected / exposed | 26 / 129 (20.16%) | 45 / 128 (35.16%) | 33 / 128 (25.78%) |
| occurrences (all)           | 105               | 106               | 95                |
| Hypoaesthesia               |                   |                   |                   |
| subjects affected / exposed | 2 / 129 (1.55%)   | 3 / 128 (2.34%)   | 2 / 128 (1.56%)   |
| occurrences (all)           | 3                 | 5                 | 2                 |
| Hypotonia                   |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 0                 | 1                 | 0                 |
| Intercostal neuralgia       |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)           | 0                 | 0                 | 1                 |
| Lethargy                    |                   |                   |                   |
| subjects affected / exposed | 2 / 129 (1.55%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 2                 | 0                 | 0                 |
| Loss of consciousness       |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 1                 | 0                 | 0                 |
| Migraine                    |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 0                 | 10                | 0                 |
| Neuralgia                   |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)           | 0                 | 0                 | 1                 |
| Neuritis                    |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)           | 0                 | 0                 | 1                 |
| Paraesthesia                |                   |                   |                   |
| subjects affected / exposed | 2 / 129 (1.55%)   | 3 / 128 (2.34%)   | 2 / 128 (1.56%)   |
| occurrences (all)           | 3                 | 4                 | 3                 |
| Postictal paralysis         |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 1                 | 0                 | 0                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Presyncope                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 4 / 128 (3.13%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 6               | 1               |
| Radiculopathy               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Sciatica                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Sensory loss                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Sinus headache              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 1               | 4               |
| Somnolence                  |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 5 / 128 (3.91%) | 0 / 128 (0.00%) |
| occurrences (all)           | 4               | 7               | 0               |
| Syncope                     |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 4 / 128 (3.13%) | 4 / 128 (3.13%) |
| occurrences (all)           | 6               | 10              | 5               |
| Tension headache            |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Tremor                      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 3 / 128 (2.34%) |
| occurrences (all)           | 0               | 0               | 4               |
| Trigeminal neuralgia        |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Trigeminal neuritis         |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Vascular encephalopathy     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |

|                                      |                 |                 |                  |
|--------------------------------------|-----------------|-----------------|------------------|
| Blood and lymphatic system disorders |                 |                 |                  |
| Anaemia                              |                 |                 |                  |
| subjects affected / exposed          | 5 / 129 (3.88%) | 3 / 128 (2.34%) | 11 / 128 (8.59%) |
| occurrences (all)                    | 6               | 3               | 15               |
| Bicytopenia                          |                 |                 |                  |
| subjects affected / exposed          | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0                |
| Blood loss anaemia                   |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0                |
| Cytopenia                            |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%)  |
| occurrences (all)                    | 0               | 1               | 1                |
| Heparin-induced thrombocytopenia     |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0                |
| Hypothrombinaemia                    |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0                |
| Increased tendency to bruise         |                 |                 |                  |
| subjects affected / exposed          | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0                |
| Leukopenia                           |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)                    | 0               | 0               | 1                |
| Lymphadenopathy                      |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%)  |
| occurrences (all)                    | 0               | 2               | 1                |
| Lymphocytosis                        |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)                    | 0               | 0               | 1                |
| Macrocytosis                         |                 |                 |                  |
| subjects affected / exposed          | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)                    | 0               | 0               | 1                |
| Pancytopenia                         |                 |                 |                  |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                            | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Polycythaemia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)        | 2 / 129 (1.55%)<br>2 | 2 / 128 (1.56%)<br>2 | 3 / 128 (2.34%)<br>3 |
| Lymphadenitis<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 129 (1.55%)<br>2 | 0 / 128 (0.00%)<br>0 | 3 / 128 (2.34%)<br>3 |
| Ear and labyrinth disorders   |                      |                      |                      |
| Cerumen impaction<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Ear congestion<br>subjects affected / exposed<br>occurrences (all)          | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Ear haemorrhage<br>subjects affected / exposed<br>occurrences (all)         | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>5 |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                | 1 / 129 (0.78%)<br>1 | 3 / 128 (2.34%)<br>3 | 1 / 128 (0.78%)<br>1 |
| Hypoacusis<br>subjects affected / exposed<br>occurrences (all)              | 3 / 129 (2.33%)<br>4 | 1 / 128 (0.78%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Mixed deafness<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Tinnitus                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 4 / 128 (3.13%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 6               | 1               |
| Vertigo                     |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 4 / 128 (3.13%) | 2 / 128 (1.56%) |
| occurrences (all)           | 2               | 4               | 2               |
| Eye disorders               |                 |                 |                 |
| Asthenopia                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Astigmatism                 |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Blepharitis                 |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Cataract                    |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences (all)           | 4               | 0               | 2               |
| Chalazion                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Chromatopsia                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences (all)           | 0               | 0               | 2               |
| Conjunctival haemorrhage    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 4               | 1               |
| Cornea verticillata         |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Corneal oedema              |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Corneal opacity             |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Dacryostenosis acquired     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Dark circles under eyes     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Diplopia                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Dry eye                     |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 1               | 1               |
| Dyschromatopsia             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Eye disorder                |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |
| Eye haemorrhage             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eye inflammation            |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Eye irritation              |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 2               | 0               | 1               |
| Eye pain                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 3 / 128 (2.34%) |
| occurrences (all)           | 0               | 0               | 6               |
| Eye pruritus                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eye swelling                |                 |                 |                 |

|                                |                 |                 |                 |
|--------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)              | 0               | 1               | 0               |
| Foreign body sensation in eyes |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)              | 0               | 5               | 0               |
| Glaucoma                       |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 2 / 128 (1.56%) |
| occurrences (all)              | 0               | 0               | 2               |
| Hypermetropia                  |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 0               | 1               |
| Keratitis                      |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 0               | 1               |
| Lacrimation increased          |                 |                 |                 |
| subjects affected / exposed    | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)              | 1               | 1               | 0               |
| Macular degeneration           |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)              | 0               | 2               | 0               |
| Maculopathy                    |                 |                 |                 |
| subjects affected / exposed    | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Ocular hyperaemia              |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 1               | 2               |
| Periorbital pain               |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 0               | 1               |
| Periorbital swelling           |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 3               | 1               |
| Photophobia                    |                 |                 |                 |
| subjects affected / exposed    | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)              | 0               | 0               | 1               |
| Photopsia                      |                 |                 |                 |

|  |                      |                       |                      |
|--|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0 |
| <b>Pterygium</b>                                 |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0  | 2 / 128 (1.56%)<br>2 |
| <b>Retinal vascular disorder</b>                 |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2  | 1 / 128 (0.78%)<br>1 |
| <b>Swelling of eyelid</b>                        |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1  | 1 / 128 (0.78%)<br>1 |
| <b>Vision blurred</b>                            |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 3 / 129 (2.33%)<br>3 | 2 / 128 (1.56%)<br>3  | 2 / 128 (1.56%)<br>2 |
| <b>Visual impairment</b>                         |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 2 / 128 (1.56%)<br>2  | 4 / 128 (3.13%)<br>5 |
| <b>Visual snow syndrome</b>                      |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0 |
| <b>Xerophthalmia</b>                             |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0  | 1 / 128 (0.78%)<br>1 |
| <b>Gastrointestinal disorders</b>                |                      |                       |                      |
| <b>Abdominal discomfort</b>                      |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 2 / 129 (1.55%)<br>2 | 1 / 128 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0 |
| <b>Abdominal distension</b>                      |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>2 | 2 / 128 (1.56%)<br>2  | 2 / 128 (1.56%)<br>2 |
| <b>Abdominal pain</b>                            |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 5 / 129 (3.88%)<br>8 | 5 / 128 (3.91%)<br>12 | 4 / 128 (3.13%)<br>6 |
| <b>Abdominal pain lower</b>                      |                      |                       |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0 |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)    | 6 / 129 (4.65%)<br>12   | 7 / 128 (5.47%)<br>29   | 11 / 128 (8.59%)<br>15  |
| Abdominal symptom<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>1    | 0 / 128 (0.00%)<br>0    | 0 / 128 (0.00%)<br>0    |
| Angular cheilitis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>1    | 0 / 128 (0.00%)<br>0    | 0 / 128 (0.00%)<br>0    |
| Ascites<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 129 (2.33%)<br>3    | 2 / 128 (1.56%)<br>2    | 1 / 128 (0.78%)<br>1    |
| Barrett's oesophagus<br>subjects affected / exposed<br>occurrences (all)    | 0 / 129 (0.00%)<br>0    | 1 / 128 (0.78%)<br>1    | 0 / 128 (0.00%)<br>0    |
| Chronic gastritis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>2    | 0 / 128 (0.00%)<br>0    | 1 / 128 (0.78%)<br>1    |
| Colitis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 129 (0.78%)<br>1    | 0 / 128 (0.00%)<br>0    | 1 / 128 (0.78%)<br>1    |
| Constipation<br>subjects affected / exposed<br>occurrences (all)            | 5 / 129 (3.88%)<br>5    | 1 / 128 (0.78%)<br>1    | 1 / 128 (0.78%)<br>1    |
| Dental necrosis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 129 (0.78%)<br>1    | 0 / 128 (0.00%)<br>0    | 0 / 128 (0.00%)<br>0    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | 13 / 129 (10.08%)<br>27 | 17 / 128 (13.28%)<br>45 | 20 / 128 (15.63%)<br>28 |
| Diverticulum intestinal<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>2    | 0 / 128 (0.00%)<br>0    | 0 / 128 (0.00%)<br>0    |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0    | 3 / 128 (2.34%)<br>4    | 3 / 128 (2.34%)<br>3    |

|   |                      |                        |                        |
|---|----------------------|------------------------|------------------------|
| Duodenal bulb deformity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Duodenal ulcer<br>subjects affected / exposed<br>occurrences (all)            | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0   |
| Duodenal vascular ectasia<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1   |
| Duodenogastric reflux<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0   |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 129 (4.65%)<br>8 | 10 / 128 (7.81%)<br>12 | 10 / 128 (7.81%)<br>24 |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0   |
| Enteritis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Enterocolitis<br>subjects affected / exposed<br>occurrences (all)             | 2 / 129 (1.55%)<br>3 | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1   |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)     | 1 / 129 (0.78%)<br>3 | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1   |
| Eructation<br>subjects affected / exposed<br>occurrences (all)                | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Faeces discoloured<br>subjects affected / exposed<br>occurrences (all)        | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 2 / 128 (1.56%)<br>4   | 0 / 128 (0.00%)<br>0   |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| Food poisoning                   |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 3 / 128 (2.34%) |
| occurrences (all)                | 1               | 2               | 4               |
| Frequent bowel movements         |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Gastric disorder                 |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 3 / 128 (2.34%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 13              | 1               |
| Gastric polyps                   |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 1               | 1               |
| Gastritis                        |                 |                 |                 |
| subjects affected / exposed      | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 3 / 128 (2.34%) |
| occurrences (all)                | 3               | 2               | 3               |
| Gastritis erosive                |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Gastrointestinal disorder        |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Gastrointestinal haemorrhage     |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 1               | 0               |
| Gastrooesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 2 / 128 (1.56%) | 4 / 128 (3.13%) |
| occurrences (all)                | 1               | 2               | 5               |
| Gingival bleeding                |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                | 2               | 0               | 1               |
| Gingival hypertrophy             |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 0               | 1               |
| Gingival pain                    |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 0               | 1               |

|                             |                   |                  |                 |
|-----------------------------|-------------------|------------------|-----------------|
| Haematochezia               |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)           | 0                 | 1                | 0               |
| Haemorrhoidal haemorrhage   |                   |                  |                 |
| subjects affected / exposed | 1 / 129 (0.78%)   | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)           | 1                 | 2                | 0               |
| Haemorrhoids                |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 2 / 128 (1.56%) |
| occurrences (all)           | 0                 | 0                | 2               |
| Hiatus hernia               |                   |                  |                 |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)           | 2                 | 0                | 1               |
| Hypoaesthesia oral          |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 2 / 128 (1.56%) |
| occurrences (all)           | 0                 | 0                | 3               |
| Intestinal haemorrhage      |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)           | 0                 | 0                | 1               |
| Intestinal polyp            |                   |                  |                 |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)           | 2                 | 0                | 0               |
| Irritable bowel syndrome    |                   |                  |                 |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)           | 1                 | 0                | 0               |
| Large intestine polyp       |                   |                  |                 |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)  | 2 / 128 (1.56%) |
| occurrences (all)           | 1                 | 0                | 2               |
| Mouth haemorrhage           |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)           | 0                 | 0                | 2               |
| Mouth ulceration            |                   |                  |                 |
| subjects affected / exposed | 0 / 129 (0.00%)   | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)           | 0                 | 1                | 0               |
| Nausea                      |                   |                  |                 |
| subjects affected / exposed | 16 / 129 (12.40%) | 12 / 128 (9.38%) | 8 / 128 (6.25%) |
| occurrences (all)           | 17                | 20               | 12              |

|                                    |                 |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|
| Odynophagia                        |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Oesophageal disorder               |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Pancreatitis                       |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                  | 0               | 1               | 2               |
| Peptic ulcer                       |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Rectal haemorrhage                 |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 1               | 0               |
| Stomatitis                         |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Tongue erythema                    |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                  | 0               | 0               | 1               |
| Tongue ulceration                  |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Toothache                          |                 |                 |                 |
| subjects affected / exposed        | 5 / 129 (3.88%) | 5 / 128 (3.91%) | 3 / 128 (2.34%) |
| occurrences (all)                  | 5               | 5               | 3               |
| Umbilical hernia                   |                 |                 |                 |
| subjects affected / exposed        | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Upper gastrointestinal haemorrhage |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Varices oesophageal                |                 |                 |                 |
| subjects affected / exposed        | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |

|   |                       |                        |                      |
|---|-----------------------|------------------------|----------------------|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                      | 7 / 129 (5.43%)<br>11 | 10 / 128 (7.81%)<br>14 | 7 / 128 (5.47%)<br>8 |
| <b>Skin and subcutaneous tissue disorders</b>                                     |                       |                        |                      |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 129 (0.00%)<br>0  | 3 / 128 (2.34%)<br>3   | 0 / 128 (0.00%)<br>0 |
| Chronic spontaneous urticaria<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0 |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 129 (0.00%)<br>0  | 1 / 128 (0.78%)<br>1   | 1 / 128 (0.78%)<br>1 |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0  | 0 / 128 (0.00%)<br>0   | 3 / 128 (2.34%)<br>3 |
| Dermatitis atopic<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0  | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0 |
| Diabetic foot<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0  | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0 |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 129 (0.78%)<br>1  | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1 |
| Eczema nummular<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0  | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1 |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 129 (1.55%)<br>31 | 4 / 128 (3.13%)<br>7   | 4 / 128 (3.13%)<br>5 |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 129 (1.55%)<br>3  | 2 / 128 (1.56%)<br>2   | 0 / 128 (0.00%)<br>0 |
| Hypersensitivity vasculitis   |                       |                        |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Photosensitivity reaction   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Pruritus                    |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 3 / 128 (2.34%) | 3 / 128 (2.34%) |
| occurrences (all)           | 5               | 3               | 3               |
| Rash                        |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)           | 7               | 1               | 3               |
| Rash erythematous           |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Rash macular                |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 1               | 1               |
| Rash papular                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Skin burning sensation      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Skin disorder               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1               | 0               | 1               |
| Skin fissures               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Skin hyperpigmentation      |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Skin irritation             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Skin lesion                 |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)             | 2 / 129 (1.55%)<br>2 | 1 / 128 (0.78%)<br>2 | 2 / 128 (1.56%)<br>2 |
| Telangiectasia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Vitiligo<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Yellow skin<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Renal and urinary disorders  |                      |                      |                      |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)    | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Azotaemia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)             | 0 / 129 (0.00%)<br>0 | 2 / 128 (1.56%)<br>3 | 0 / 128 (0.00%)<br>0 |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)            | 1 / 129 (0.78%)<br>1 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |
| Pyelocaliectasis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal cyst                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 1 / 128 (0.78%) | 3 / 128 (2.34%) |
| occurrences (all)                               | 3               | 1               | 3               |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                               | 1               | 2               | 3               |
| Renal impairment                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 2 / 128 (1.56%) |
| occurrences (all)                               | 1               | 1               | 2               |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Endocrine disorders                             |                 |                 |                 |
| Autoimmune thyroiditis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Cushing's syndrome                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Hyperthyroidism                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Hypothyroidism                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 129 (1.55%) | 4 / 128 (3.13%) | 2 / 128 (1.56%) |
| occurrences (all)                               | 2               | 4               | 2               |
| Inappropriate antidiuretic hormone secretion    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 1               | 0               | 0               |
| Primary hypothyroidism                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Thyroid mass                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                               | 0               | 1               | 0               |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |

|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| Arthralgia                  |                   |                   |                   |
| subjects affected / exposed | 14 / 129 (10.85%) | 13 / 128 (10.16%) | 15 / 128 (11.72%) |
| occurrences (all)           | 17                | 19                | 24                |
| Arthritis                   |                   |                   |                   |
| subjects affected / exposed | 3 / 129 (2.33%)   | 3 / 128 (2.34%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 3                 | 4                 | 0                 |
| Back pain                   |                   |                   |                   |
| subjects affected / exposed | 16 / 129 (12.40%) | 10 / 128 (7.81%)  | 14 / 128 (10.94%) |
| occurrences (all)           | 20                | 24                | 23                |
| Bone pain                   |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 2 / 128 (1.56%)   | 1 / 128 (0.78%)   |
| occurrences (all)           | 0                 | 6                 | 1                 |
| Bursitis                    |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 0                 | 2                 | 0                 |
| Gouty arthritis             |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 1                 | 0                 | 0                 |
| Joint swelling              |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 1 / 128 (0.78%)   | 2 / 128 (1.56%)   |
| occurrences (all)           | 2                 | 1                 | 2                 |
| Limb mass                   |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 2                 | 0                 | 0                 |
| Metatarsalgia               |                   |                   |                   |
| subjects affected / exposed | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)           | 0                 | 0                 | 1                 |
| Muscle contracture          |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 1                 | 0                 | 0                 |
| Muscle spasms               |                   |                   |                   |
| subjects affected / exposed | 4 / 129 (3.10%)   | 3 / 128 (2.34%)   | 3 / 128 (2.34%)   |
| occurrences (all)           | 5                 | 5                 | 5                 |
| Muscular weakness           |                   |                   |                   |
| subjects affected / exposed | 1 / 129 (0.78%)   | 2 / 128 (1.56%)   | 0 / 128 (0.00%)   |
| occurrences (all)           | 1                 | 2                 | 0                 |

|  |                      |                        |                        |
|--|----------------------|------------------------|------------------------|
| Musculoskeletal discomfort<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1   | 0 / 128 (0.00%)<br>0   |
| Musculoskeletal disorder<br>subjects affected / exposed<br>occurrences (all)   | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 4 / 129 (3.10%)<br>4 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>3   | 1 / 128 (0.78%)<br>1   |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 129 (3.10%)<br>5 | 10 / 128 (7.81%)<br>16 | 12 / 128 (9.38%)<br>17 |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 129 (0.00%)<br>0 | 3 / 128 (2.34%)<br>4   | 4 / 128 (3.13%)<br>4   |
| Osteitis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 1 / 128 (0.78%)<br>1   |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 129 (0.78%)<br>1 | 2 / 128 (1.56%)<br>3   | 3 / 128 (2.34%)<br>3   |
| Osteochondrosis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 129 (1.55%)<br>2 | 1 / 128 (0.78%)<br>1   | 4 / 128 (3.13%)<br>4   |
| Osteopenia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1   | 1 / 128 (0.78%)<br>1   |
| Osteoporosis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 129 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1   | 1 / 128 (0.78%)<br>1   |
| Osteoporotic fracture<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0   | 0 / 128 (0.00%)<br>0   |

|                              |                 |                   |                 |
|------------------------------|-----------------|-------------------|-----------------|
| Pain in extremity            |                 |                   |                 |
| subjects affected / exposed  | 6 / 129 (4.65%) | 14 / 128 (10.94%) | 6 / 128 (4.69%) |
| occurrences (all)            | 7               | 17                | 13              |
| Pain in jaw                  |                 |                   |                 |
| subjects affected / exposed  | 3 / 129 (2.33%) | 3 / 128 (2.34%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 3               | 3                 | 2               |
| Pathological fracture        |                 |                   |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0                 | 1               |
| Plantar fasciitis            |                 |                   |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0                 | 1               |
| Polymyalgia rheumatica       |                 |                   |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 0                 | 0               |
| Rheumatoid arthritis         |                 |                   |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0                 | 1               |
| Sclerodactylia               |                 |                   |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)            | 1               | 0                 | 0               |
| Scleroderma                  |                 |                   |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 0 / 128 (0.00%) |
| occurrences (all)            | 2               | 0                 | 0               |
| Sjogren's syndrome           |                 |                   |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 0                 | 1               |
| Spinal disorder              |                 |                   |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 0 / 128 (0.00%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 2               | 0                 | 1               |
| Spinal pain                  |                 |                   |                 |
| subjects affected / exposed  | 1 / 129 (0.78%) | 3 / 128 (2.34%)   | 0 / 128 (0.00%) |
| occurrences (all)            | 2               | 4                 | 0               |
| Systemic lupus erythematosus |                 |                   |                 |
| subjects affected / exposed  | 0 / 129 (0.00%) | 1 / 128 (0.78%)   | 1 / 128 (0.78%) |
| occurrences (all)            | 0               | 1                 | 1               |

|  |                  |                  |                 |
|--|------------------|------------------|-----------------|
| Systemic scleroderma                       |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 2 / 128 (1.56%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 0                | 3                | 0               |
| Temporomandibular joint syndrome           |                  |                  |                 |
| subjects affected / exposed                | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 1                | 0                | 0               |
| Tendonitis                                 |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 0                | 3                | 0               |
| Trigger finger                             |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 0                | 1                | 0               |
| Undifferentiated connective tissue disease |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 1 / 128 (0.78%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 0                | 1                | 0               |
| Infections and infestations                |                  |                  |                 |
| Abdominal abscess                          |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)                          | 0                | 0                | 1               |
| Acute sinusitis                            |                  |                  |                 |
| subjects affected / exposed                | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 3 / 128 (2.34%) |
| occurrences (all)                          | 1                | 0                | 3               |
| Bacterial disease carrier                  |                  |                  |                 |
| subjects affected / exposed                | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)                          | 1                | 0                | 1               |
| Bacterial infection                        |                  |                  |                 |
| subjects affected / exposed                | 0 / 129 (0.00%)  | 0 / 128 (0.00%)  | 1 / 128 (0.78%) |
| occurrences (all)                          | 0                | 0                | 1               |
| Bacterial rhinitis                         |                  |                  |                 |
| subjects affected / exposed                | 1 / 129 (0.78%)  | 0 / 128 (0.00%)  | 0 / 128 (0.00%) |
| occurrences (all)                          | 1                | 0                | 0               |
| Bronchitis                                 |                  |                  |                 |
| subjects affected / exposed                | 11 / 129 (8.53%) | 11 / 128 (8.59%) | 8 / 128 (6.25%) |
| occurrences (all)                          | 16               | 11               | 8               |
| Bronchitis viral                           |                  |                  |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| COVID-19                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| COVID-19 pneumonia          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Cellulitis                  |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 1 / 128 (0.78%) |
| occurrences (all)           | 3               | 2               | 1               |
| Chronic sinusitis           |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Chronic tonsillitis 0 0     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Conjunctivitis              |                 |                 |                 |
| subjects affected / exposed | 5 / 129 (3.88%) | 1 / 128 (0.78%) | 6 / 128 (4.69%) |
| occurrences (all)           | 5               | 1               | 7               |
| Cystitis                    |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)           | 4               | 3               | 0               |
| Device related infection    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Device related sepsis       |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Diverticulitis              |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Ear infection               |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 5               | 1               | 0               |
| Enteritis infectious        |                 |                 |                 |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Erysipelas                       |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Eye infection                    |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 0               | 1               |
| Gastric infection                |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Gastroenteritis                  |                 |                 |                 |
| subjects affected / exposed      | 4 / 129 (3.10%) | 1 / 128 (0.78%) | 3 / 128 (2.34%) |
| occurrences (all)                | 5               | 1               | 3               |
| Gastroenteritis viral            |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 4               | 0               |
| Gastrointestinal candidiasis     |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)                | 0               | 0               | 1               |
| Gastrointestinal infection       |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Gastrointestinal viral infection |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 1               | 0               |
| Genital infection female         |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Gingivitis                       |                 |                 |                 |
| subjects affected / exposed      | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Groin abscess                    |                 |                 |                 |
| subjects affected / exposed      | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Helicobacter gastritis           |                 |                 |                 |

|                             |                 |                 |                  |
|-----------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)           | 2               | 0               | 1                |
| Helicobacter infection      |                 |                 |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0                |
| Hepatitis B                 |                 |                 |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0                |
| Herpes simplex              |                 |                 |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 2 / 128 (1.56%)  |
| occurrences (all)           | 1               | 8               | 2                |
| Herpes virus infection      |                 |                 |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 1               | 1               | 0                |
| Herpes zoster               |                 |                 |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)           | 0               | 0               | 1                |
| Hordeolum                   |                 |                 |                  |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0                |
| Incision site abscess       |                 |                 |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0                |
| Infection                   |                 |                 |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%)  |
| occurrences (all)           | 0               | 1               | 1                |
| Influenza                   |                 |                 |                  |
| subjects affected / exposed | 6 / 129 (4.65%) | 8 / 128 (6.25%) | 11 / 128 (8.59%) |
| occurrences (all)           | 7               | 12              | 16               |
| Joint abscess               |                 |                 |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0                |
| Laryngitis                  |                 |                 |                  |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 2 / 128 (1.56%)  |
| occurrences (all)           | 0               | 2               | 2                |
| Localised infection         |                 |                 |                  |

|                                   |                   |                   |                   |
|-----------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed       | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 2 / 128 (1.56%)   |
| occurrences (all)                 | 0                 | 1                 | 2                 |
| Lower respiratory tract infection |                   |                   |                   |
| subjects affected / exposed       | 2 / 129 (1.55%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 2                 | 0                 | 0                 |
| Nasopharyngitis                   |                   |                   |                   |
| subjects affected / exposed       | 19 / 129 (14.73%) | 16 / 128 (12.50%) | 19 / 128 (14.84%) |
| occurrences (all)                 | 44                | 34                | 40                |
| Oesophageal candidiasis           |                   |                   |                   |
| subjects affected / exposed       | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 0                 | 1                 | 0                 |
| Onychomycosis                     |                   |                   |                   |
| subjects affected / exposed       | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)                 | 1                 | 0                 | 1                 |
| Oral candidiasis                  |                   |                   |                   |
| subjects affected / exposed       | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 2 / 128 (1.56%)   |
| occurrences (all)                 | 1                 | 0                 | 4                 |
| Oral fungal infection             |                   |                   |                   |
| subjects affected / exposed       | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 0                 | 1                 | 0                 |
| Oral herpes                       |                   |                   |                   |
| subjects affected / exposed       | 2 / 129 (1.55%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)                 | 2                 | 0                 | 1                 |
| Otitis media                      |                   |                   |                   |
| subjects affected / exposed       | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 | 0                 |
| Otitis media chronic              |                   |                   |                   |
| subjects affected / exposed       | 1 / 129 (0.78%)   | 0 / 128 (0.00%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 | 0                 |
| Paronychia                        |                   |                   |                   |
| subjects affected / exposed       | 0 / 129 (0.00%)   | 1 / 128 (0.78%)   | 0 / 128 (0.00%)   |
| occurrences (all)                 | 0                 | 1                 | 0                 |
| Periodontitis                     |                   |                   |                   |
| subjects affected / exposed       | 0 / 129 (0.00%)   | 0 / 128 (0.00%)   | 1 / 128 (0.78%)   |
| occurrences (all)                 | 0                 | 0                 | 1                 |
| Pharyngitis                       |                   |                   |                   |

|                                   |                 |                 |                  |
|-----------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed       | 1 / 129 (0.78%) | 0 / 128 (0.00%) | 3 / 128 (2.34%)  |
| occurrences (all)                 | 1               | 0               | 4                |
| Pharyngitis bacterial             |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)                 | 0               | 1               | 0                |
| Pneumonia                         |                 |                 |                  |
| subjects affected / exposed       | 5 / 129 (3.88%) | 3 / 128 (2.34%) | 5 / 128 (3.91%)  |
| occurrences (all)                 | 5               | 3               | 6                |
| Pulpitis dental                   |                 |                 |                  |
| subjects affected / exposed       | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 1 / 128 (0.78%)  |
| occurrences (all)                 | 1               | 1               | 1                |
| Pyelonephritis chronic            |                 |                 |                  |
| subjects affected / exposed       | 1 / 129 (0.78%) | 1 / 128 (0.78%) | 0 / 128 (0.00%)  |
| occurrences (all)                 | 1               | 1               | 0                |
| Respiratory tract infection       |                 |                 |                  |
| subjects affected / exposed       | 5 / 129 (3.88%) | 4 / 128 (3.13%) | 6 / 128 (4.69%)  |
| occurrences (all)                 | 9               | 4               | 6                |
| Respiratory tract infection viral |                 |                 |                  |
| subjects affected / exposed       | 4 / 129 (3.10%) | 5 / 128 (3.91%) | 8 / 128 (6.25%)  |
| occurrences (all)                 | 4               | 6               | 13               |
| Rhinitis                          |                 |                 |                  |
| subjects affected / exposed       | 5 / 129 (3.88%) | 5 / 128 (3.91%) | 1 / 128 (0.78%)  |
| occurrences (all)                 | 5               | 8               | 1                |
| Salpingo-oophoritis               |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Sinusitis                         |                 |                 |                  |
| subjects affected / exposed       | 3 / 129 (2.33%) | 3 / 128 (2.34%) | 10 / 128 (7.81%) |
| occurrences (all)                 | 7               | 6               | 16               |
| Skin infection                    |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 1 / 128 (0.78%)  |
| occurrences (all)                 | 0               | 1               | 1                |
| Tinea pedis                       |                 |                 |                  |
| subjects affected / exposed       | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%)  |
| occurrences (all)                 | 0               | 0               | 1                |
| Tongue fungal infection           |                 |                 |                  |

|   |                   |                 |                   |
|---|-------------------|-----------------|-------------------|
| subjects affected / exposed             | 1 / 129 (0.78%)   | 0 / 128 (0.00%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 2                 | 0               | 0                 |
| Tonsillitis                             |                   |                 |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)   | 3 / 128 (2.34%) | 1 / 128 (0.78%)   |
| occurrences (all)                       | 2                 | 3               | 1                 |
| Tonsillitis bacterial                   |                   |                 |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)   | 1 / 128 (0.78%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                 | 1               | 0                 |
| Tooth abscess                           |                   |                 |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)   | 0 / 128 (0.00%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                 | 0               | 0                 |
| Tracheitis                              |                   |                 |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)   | 0 / 128 (0.00%) | 1 / 128 (0.78%)   |
| occurrences (all)                       | 4                 | 0               | 1                 |
| Tracheobronchitis                       |                   |                 |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)   | 1 / 128 (0.78%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                 | 1               | 0                 |
| Upper respiratory tract infection       |                   |                 |                   |
| subjects affected / exposed             | 16 / 129 (12.40%) | 8 / 128 (6.25%) | 13 / 128 (10.16%) |
| occurrences (all)                       | 41                | 9               | 27                |
| Urinary tract infection                 |                   |                 |                   |
| subjects affected / exposed             | 4 / 129 (3.10%)   | 1 / 128 (0.78%) | 5 / 128 (3.91%)   |
| occurrences (all)                       | 4                 | 2               | 5                 |
| Vaginal infection                       |                   |                 |                   |
| subjects affected / exposed             | 1 / 129 (0.78%)   | 1 / 128 (0.78%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 1                 | 1               | 0                 |
| Varicella                               |                   |                 |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)   | 0 / 128 (0.00%) | 1 / 128 (0.78%)   |
| occurrences (all)                       | 0                 | 0               | 1                 |
| Viral infection                         |                   |                 |                   |
| subjects affected / exposed             | 4 / 129 (3.10%)   | 5 / 128 (3.91%) | 3 / 128 (2.34%)   |
| occurrences (all)                       | 5                 | 5               | 3                 |
| Viral rhinitis                          |                   |                 |                   |
| subjects affected / exposed             | 0 / 129 (0.00%)   | 1 / 128 (0.78%) | 0 / 128 (0.00%)   |
| occurrences (all)                       | 0                 | 1               | 0                 |
| Viral upper respiratory tract infection |                   |                 |                   |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                               | 1 / 129 (0.78%)<br>1 | 2 / 128 (1.56%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Vulvovaginal candidiasis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| <b>Metabolism and nutrition disorders</b>                                      |                      |                      |                      |
| Cachexia<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Calcium deficiency<br>subjects affected / exposed<br>occurrences (all)         | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)         | 2 / 129 (1.55%)<br>6 | 2 / 128 (1.56%)<br>2 | 2 / 128 (1.56%)<br>3 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 2 / 128 (1.56%)<br>2 | 0 / 128 (0.00%)<br>0 |
| Fluid overload<br>subjects affected / exposed<br>occurrences (all)             | 2 / 129 (1.55%)<br>2 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |
| Fluid retention<br>subjects affected / exposed<br>occurrences (all)            | 2 / 129 (1.55%)<br>2 | 1 / 128 (0.78%)<br>1 | 2 / 128 (1.56%)<br>2 |
| Glucose tolerance impaired<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 128 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 |
| Gout<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 129 (1.55%)<br>2 | 2 / 128 (1.56%)<br>2 | 1 / 128 (0.78%)<br>1 |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 0 / 128 (0.00%)<br>0 | 1 / 128 (0.78%)<br>1 |

|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| Hyperglycaemia              |                  |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 1                | 1               | 0               |
| Hyperkalaemia               |                  |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%)  | 4 / 128 (3.13%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2                | 4               | 0               |
| Hyperlipidaemia             |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0                | 0               | 1               |
| Hypernatraemia              |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0                | 1               | 0               |
| Hyperuricaemia              |                  |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%)  | 1 / 128 (0.78%) | 3 / 128 (2.34%) |
| occurrences (all)           | 3                | 1               | 3               |
| Hypocalcaemia               |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0                | 1               | 0               |
| Hypoglycaemia               |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0                | 1               | 0               |
| Hypokalaemia                |                  |                 |                 |
| subjects affected / exposed | 10 / 129 (7.75%) | 6 / 128 (4.69%) | 5 / 128 (3.91%) |
| occurrences (all)           | 12               | 9               | 7               |
| Hypomagnesaemia             |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 1 / 128 (0.78%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0                | 1               | 2               |
| Hyponatraemia               |                  |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%)  | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 1                | 0               | 1               |
| Impaired fasting glucose    |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0                | 0               | 1               |
| Insulin resistance          |                  |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%)  | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0                | 0               | 1               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Iron deficiency             |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 3 / 128 (2.34%) | 2 / 128 (1.56%) |
| occurrences (all)           | 0               | 3               | 2               |
| Mineral metabolism disorder |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 128 (0.00%) | 1 / 128 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Obesity                     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 128 (1.56%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Steroid diabetes            |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 128 (0.00%) | 0 / 128 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Vitamin D deficiency        |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 128 (0.78%) | 0 / 128 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 18 November 2014 | Permit short term phosphodiesterase type 5 inhibitor (PDE5I) use prior to enrollment.<br>Allow temporary discontinuation (up to 14 days) of study treatment to permit temporary treatment with prohibited medications for comorbidities.<br>Addition of riociguat as a prohibited medication. |
| 28 August 2020   | To increase, in a blinded manner, the dose for subjects receiving 5 mg (TID) to 20 mg (TID), the approved dose in these 5 countries.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Study stopped by DMC after first IA (primary objective met). OS and clinical worsening (CW) sig level adjusted for IA (99.7% CIs used instead of 95% CIs). OS 80mg v 5mg primary, CW 80mg v 5mg key secondary. Other comparisons / endpoints are nominal.

Notes: