



## Clinical trial results:

**Efficacy and safety of 3 doses of S 47445 versus placebo in patients with Alzheimer's disease at mild to moderate stages with depressive symptoms. A 24-week international, multi-centre, randomized, double-blind, placebo-controlled phase II study in monotherapy followed by an optional 28-week extension period in co-administration with donepezil.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-001519-38    |
| Trial protocol           | DE CZ HU BG SK    |
| Global end of trial date | 20 September 2017 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 18 July 2018 |
| First version publication date | 18 July 2018 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CL2-47445-011 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02626572     |
| WHO universal trial number (UTN)   | U1111-1156-1378 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Institut de Recherches Internationales Servier   |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284   |
| Public contact               | Clinical Studies Department, Institut de Recherches Internationales Servier, 33 0155724366, clinicaltrials@servier.com |
| Scientific contact           | Clinical Studies Department, Institut de Recherches Internationales Servier, 33 0155724366, clinicaltrials@servier.com |

Notes:

### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 20 September 2017 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 20 September 2017 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 20 September 2017 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

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**General information about the trial**

Main objective of the trial:

Assessment of efficacy of 3 doses of S 47445 versus placebo on cognitive performance measured with the 11-item ADAS-Cog after 24 weeks of treatment.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 13 February 2015 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 37             |
| Country: Number of subjects enrolled | Slovakia: 11           |
| Country: Number of subjects enrolled | Bulgaria: 56           |
| Country: Number of subjects enrolled | Czech Republic: 66     |
| Country: Number of subjects enrolled | Germany: 32            |
| Country: Number of subjects enrolled | Hungary: 63            |
| Country: Number of subjects enrolled | Brazil: 48             |
| Country: Number of subjects enrolled | Chile: 83              |
| Country: Number of subjects enrolled | Japan: 4               |
| Country: Number of subjects enrolled | Mexico: 28             |
| Country: Number of subjects enrolled | Russian Federation: 73 |
| Country: Number of subjects enrolled | South Africa: 19       |
| Worldwide total number of subjects   | 520                    |
| EEA total number of subjects         | 265                    |

Notes:

**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)                      | 100 |
| From 65 to 84 years                       | 415 |
| 85 years and over                         | 5   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Male or female patients aged from 55 to 85 years suffering from mild to moderate Alzheimer's disease (AD) with depressive symptoms.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | 24-week treatment period (overall period)                     |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | S 47445 5 mg |

Arm description: -

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | S 47445 5 mg       |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

1 tablet of S47445 5 mg was administered once a day during breakfast with a glass of water.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | S 47445 15 mg |
|------------------|---------------|

Arm description: -

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | S 47445 15 mg      |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

1 tablet of S47445 15 mg was administered once a day during breakfast with a glass of water.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | S 47445 50 mg |
|------------------|---------------|

Arm description: -

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | S 47445 50 mg      |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

1 tablet of S47445 50 mg was administered once a day during breakfast with a glass of water.

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

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

Dosage and administration details:

1 tablet of placebo was administered once a day during breakfast with a glass of water.

| <b>Number of subjects in period 1</b> | S 47445 5 mg | S 47445 15 mg | S 47445 50 mg |
|---------------------------------------|--------------|---------------|---------------|
| Started                               | 129          | 130           | 132           |
| Completed                             | 120          | 116           | 116           |
| Not completed                         | 9            | 14            | 16            |
| Adverse event, serious fatal          | -            | 1             | 2             |
| Adverse event, non-fatal              | 1            | 5             | 5             |
| Lost to follow-up                     | 1            | -             | -             |
| Non-medical reason                    | 6            | 7             | 5             |
| Lack of efficacy                      | 1            | 1             | 3             |
| Protocol deviation                    | -            | -             | 1             |

| <b>Number of subjects in period 1</b> | Placebo |
|---------------------------------------|---------|
| Started                               | 129     |
| Completed                             | 119     |
| Not completed                         | 10      |
| Adverse event, serious fatal          | 3       |
| Adverse event, non-fatal              | 3       |
| Lost to follow-up                     | -       |
| Non-medical reason                    | 4       |
| Lack of efficacy                      | -       |
| Protocol deviation                    | -       |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | S 47445 5 mg  |
| Reporting group description: - |               |
| Reporting group title          | S 47445 15 mg |
| Reporting group description: - |               |
| Reporting group title          | S 47445 50 mg |
| Reporting group description: - |               |
| Reporting group title          | Placebo       |
| Reporting group description: - |               |

| Reporting group values             | S 47445 5 mg | S 47445 15 mg | S 47445 50 mg |
|------------------------------------|--------------|---------------|---------------|
| Number of subjects                 | 129          | 130           | 132           |
| Age categorical<br>Units: Subjects |              |               |               |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 72.2<br>± 7.3 | 71.7<br>± 7.7 | 71.8<br>± 6.6 |
| Gender categorical<br>Units: Subjects                                   |               |               |               |
| Female  | 82            | 96            | 95            |
| Male  | 47            | 34            | 37            |

| Reporting group values             | Placebo | Total |  |
|------------------------------------|---------|-------|--|
| Number of subjects                 | 129     | 520   |  |
| Age categorical<br>Units: Subjects |         |       |  |

|   |               |     |  |
|---|---------------|-----|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 71.4<br>± 7.7 | -   |  |
| Gender categorical<br>Units: Subjects                                   |               |     |  |
| Female  | 90            | 363 |  |
| Male  | 39            | 157 |  |

## End points

### End points reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | S 47445 5 mg  |
| Reporting group description: - |               |
| Reporting group title          | S 47445 15 mg |
| Reporting group description: - |               |
| Reporting group title          | S 47445 50 mg |
| Reporting group description: - |               |
| Reporting group title          | Placebo       |
| Reporting group description: - |               |

### Primary: 11-item ADAS-Cog total score

|   |                              |
|---|------------------------------|
| End point title   | 11-item ADAS-Cog total score |
| End point description:  |                              |
| End point type  | Primary                      |
| End point timeframe:  |                              |
| The main analytical approach was the change from baseline to week 24. |                              |

| End point values                     | S 47445 5 mg    | S 47445 15 mg   | S 47445 50 mg   | Placebo         |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 120             | 118             | 121             | 121             |
| Units: No unit                       |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | -0.20 (± 4.91)  | -0.74 (± 5.43)  | -0.05 (± 5.82)  | 0.35 (± 5.53)   |

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Primary analysis               |
| Statistical analysis description:  |                                |
| All the longitudinal observations at each post-baseline visit during the 24-week treatment period were considered. |                                |
| Comparison groups  | S 47445 5 mg v Placebo         |
| Number of subjects included in analysis  | 241                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| Parameter estimate   | Mean difference (final values) |
| Point estimate   | -0.47                          |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | -1.83                          |
| upper limit  | 0.89                           |

|                      |                    |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
| Dispersion value     | 0.69               |

|                                   |                  |
|-----------------------------------|------------------|
| <b>Statistical analysis title</b> | Primary analysis |
|-----------------------------------|------------------|

Statistical analysis description:

All the longitudinal observations at each post-baseline visit during the 24-week treatment period were considered.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | S 47445 15 mg v Placebo        |
| Number of subjects included in analysis | 239                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.9                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.26                          |
| upper limit                             | 0.46                           |
| Variability estimate                    | Standard deviation             |
| Dispersion value                        | 0.69                           |

|                                   |                  |
|-----------------------------------|------------------|
| <b>Statistical analysis title</b> | Primary analysis |
|-----------------------------------|------------------|

Statistical analysis description:

All the longitudinal observations at each post-baseline visit during the 24-week treatment period were considered.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | S 47445 50 mg v Placebo        |
| Number of subjects included in analysis | 242                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.34                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.7                           |
| upper limit                             | 1.01                           |
| Variability estimate                    | Standard deviation             |
| Dispersion value                        | 0.69                           |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious during the treatment periods defined as below.

Adverse event reporting additional description:

Between the first and the last study drug intake date (both included) during the 24-week mandatory treatment period,

Between the first and the last study drug intake + 15 days (both included) during the 28-week optional extension treatment period and during the 52-week treatment period.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20     |

### Reporting groups

|                                |                         |
|--------------------------------|-------------------------|
| Reporting group title          | S 47445 5 mg - W0-W24   |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 15 mg - W0-W24  |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 50 mg - W0-W24  |
| Reporting group description: - |                         |
| Reporting group title          | Placebo - W0-W24        |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 5 mg - W24-W52  |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 15 mg - W24-W52 |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 50 mg - W24-W52 |
| Reporting group description: - |                         |
| Reporting group title          | Placebo - W24-W52       |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 5 mg - W0-W52   |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 15 mg - W0-W52  |
| Reporting group description: - |                         |
| Reporting group title          | S 47445 50 mg - W0-W52  |
| Reporting group description: - |                         |
| Reporting group title          | Placebo - W0-W52        |
| Reporting group description: - |                         |

| Serious adverse events                            | S 47445 5 mg - W0-W24 | S 47445 15 mg - W0-W24 | S 47445 50 mg - W0-W24 |
|---|-----------------------|------------------------|------------------------|
| Total subjects affected by serious adverse events |                       |                        |                        |
| subjects affected / exposed                       | 4 / 129 (3.10%)       | 11 / 130 (8.46%)       | 5 / 132 (3.79%)        |
| number of deaths (all causes)                     | 0                     | 0                      | 1                      |
| number of deaths resulting from adverse events    |                       |                        | 1                      |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Basal cell carcinoma  |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive breast carcinoma   |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Oropharyngeal cancer stage IV                                       |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer   |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Tonsil cancer   |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders  |                 |                 |                 |
| Hypertension  |                 |                 |                 |
| subjects affected / exposed   | 1 / 129 (0.78%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Hypertensive crisis   |                 |                 |                 |
| subjects affected / exposed   | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension   |                 |                 |                 |
| subjects affected / exposed   | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Gait disturbance                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical health deterioration                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                 |                 |                 |
| Cystocele  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Bronchitis chronic                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Aggression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 130 (1.54%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delusion  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination, visual                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Major depression                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Middle insomnia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood creatine phosphokinase increased          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Electrocardiogram abnormal                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Brain contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 129 (2.33%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seroma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subcutaneous haematoma                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic intracranial haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve sclerosis                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Tricuspid valve incompetence                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amimia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradykinesia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cogwheel rigidity                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia with Lewy bodies                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural hygroma                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 19       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |
| Blood and lymphatic system disorders            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Haemorrhagic anaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Macular degeneration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal discomfort                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| 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>Musculoskeletal and connective tissue disorders</b> |                 |                 |                 |
| Lumbar spinal stenosis                                 |                 |                 |                 |
| subjects affected / exposed                            | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |
| Osteoarthritis   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Pain in extremity                                      |                 |                 |                 |
| subjects affected / exposed                            | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>                     |                 |                 |                 |
| Diverticulitis   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Mastoiditis  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Otitis media   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia  |                 |                 |                 |
| subjects affected / exposed                            | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (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>Serious adverse events</b>                                       | Placebo - W0-W24 | S 47445 5 mg - W24-W52 | S 47445 15 mg - W24-W52 |
|---|------------------|------------------------|-------------------------|
| Total subjects affected by serious adverse events                   |                  |                        |                         |
| subjects affected / exposed   | 6 / 129 (4.65%)  | 8 / 119 (6.72%)        | 16 / 115 (13.91%)       |
| number of deaths (all causes)                                       | 1                | 0                      | 1                       |
| number of deaths resulting from adverse events                      | 1                |                        | 1                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                        |                         |
| Basal cell carcinoma  |                  |                        |                         |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 1 / 119 (0.84%)        | 0 / 115 (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                   |
| Invasive breast carcinoma   |                  |                        |                         |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 119 (0.00%)        | 1 / 115 (0.87%)         |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0                  | 0 / 1                   |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                  | 0 / 0                   |
| Oropharyngeal cancer stage IV                                       |                  |                        |                         |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 119 (0.00%)        | 0 / 115 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0                  | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                  | 0 / 0                   |
| Prostate cancer   |                  |                        |                         |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 1 / 119 (0.84%)        | 0 / 115 (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                   |
| Tonsil cancer   |                  |                        |                         |
| subjects affected / exposed   | 0 / 129 (0.00%)  | 0 / 119 (0.00%)        | 0 / 115 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0                  | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                  | 0 / 0                   |
| Vascular disorders  |                  |                        |                         |
| Hypertension  |                  |                        |                         |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Gait disturbance                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical health deterioration                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Cystocele                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Bronchitis chronic                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Aggression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (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           |
| Anxiety   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (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           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination, visual                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Major depression                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Middle insomnia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (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           |
| Suicidal ideation                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Investigations</b>                                 |                 |                 |                 |
| Blood creatine phosphokinase increased                |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Electrocardiogram abnormal                            |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| Brain contusion                                       |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 6 / 115 (5.22%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 6           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture   |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                      |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 2 / 115 (1.74%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower limb fracture                                   |                 |                 |                 |
| subjects affected / exposed                           | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seroma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subcutaneous haematoma                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic intracranial haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 2 / 115 (1.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Aortic valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| 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 failure chronic                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Mitral valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Tricuspid valve incompetence                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amimia  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Bradykinesia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Cogwheel rigidity                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Coma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia with Lewy bodies                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural hygroma                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 2 / 119 (1.68%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| alternative dictionary used: MedDRA 19          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Haemorrhagic anaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Macular degeneration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal discomfort                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (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           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Duodenal ulcer haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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           |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (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                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |   |   |   |
|---|---|---|---|
| Infections and infestations<br>Diverticulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0 |
| Mastoiditis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 115 (0.87%)<br>0 / 1<br>0 / 0     |
| Otitis media<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 115 (0.87%)<br>0 / 1<br>0 / 0     |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                     | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0     |
| Postoperative wound infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0     |
| Pyelonephritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | <br>1 / 129 (0.78%)<br>0 / 1<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0     |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                   | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0     |
| Sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br>0 / 129 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 119 (0.00%)<br>0 / 0<br>0 / 0     | <br>0 / 115 (0.00%)<br>0 / 0<br>0 / 0     |
| Septic shock  |   |   |   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| 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>Serious adverse events</b>                                       | S 47445 50 mg - W24-W52 | Placebo - W24-W52 | S 47445 5 mg - W0-W52 |
|---|-------------------------|-------------------|-----------------------|
| Total subjects affected by serious adverse events                   |                         |                   |                       |
| subjects affected / exposed   | 10 / 115 (8.70%)        | 10 / 119 (8.40%)  | 11 / 129 (8.53%)      |
| number of deaths (all causes)                                       | 1                       | 2                 | 0                     |
| number of deaths resulting from adverse events                      | 1                       | 2                 |                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                   |                       |
| Basal cell carcinoma  |                         |                   |                       |
| subjects affected / exposed   | 1 / 115 (0.87%)         | 0 / 119 (0.00%)   | 1 / 129 (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                 |
| Invasive breast carcinoma   |                         |                   |                       |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Oropharyngeal cancer stage IV                        |                 |                 |                 |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Prostate cancer                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Tonsil cancer  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Vascular disorders                                   |                 |                 |                 |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Fatigue   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gait disturbance                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical health deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Multiple organ dysfunction syndrome             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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        |                 |                 |                 |
| Cystocele                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Bronchitis chronic                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Aggression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination, visual                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Major depression                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Middle insomnia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood creatine phosphokinase increased          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Electrocardiogram abnormal                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Brain contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 2 / 119 (1.68%) | 3 / 129 (2.33%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seroma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Subcutaneous haematoma                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Traumatic intracranial haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 2 / 119 (1.68%) | 0 / 129 (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 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cardiac failure chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tricuspid valve incompetence                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amimia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradykinesia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cogwheel rigidity                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia with Lewy bodies                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Haemorrhagic stroke                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural hygroma                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 3 / 129 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| alternative dictionary used: MedDRA 19          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Haemorrhagic anaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Macular degeneration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal discomfort                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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 erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| disorders                                       |                 |                 |                 |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (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           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Infections and infestations                     |                 |                 |                 |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (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           |
| Mastoiditis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Otitis media                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 1 / 129 (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           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                       | <b>S 47445 15 mg - W0-W52</b> | <b>S 47445 50 mg - W0-W52</b> | <b>Placebo - W0-W52</b> |
|---|-------------------------------|-------------------------------|-------------------------|
| Total subjects affected by serious adverse events                   |                               |                               |                         |
| subjects affected / exposed   | 27 / 130 (20.77%)             | 16 / 132 (12.12%)             | 17 / 129 (13.18%)       |
| number of deaths (all causes)                                       | 1                             | 2                             | 3                       |
| number of deaths resulting from adverse events                      | 1                             | 2                             | 3                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |                               |                         |
| Basal cell carcinoma  |                               |                               |                         |
| subjects affected / exposed   | 0 / 130 (0.00%)               | 1 / 132 (0.76%)               | 0 / 129 (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                   |
| Invasive breast carcinoma   |                               |                               |                         |
| subjects affected / exposed   | 1 / 130 (0.77%)               | 0 / 132 (0.00%)               | 0 / 129 (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                   |
| Oropharyngeal cancer stage IV                                       |                               |                               |                         |
| subjects affected / exposed   | 0 / 130 (0.00%)               | 1 / 132 (0.76%)               | 0 / 129 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 0                         | 0 / 1                         | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0                         | 0 / 0                   |
| Prostate cancer   |                               |                               |                         |
| subjects affected / exposed   | 0 / 130 (0.00%)               | 0 / 132 (0.00%)               | 0 / 129 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 0                         | 0 / 0                         | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0                         | 0 / 0                   |
| Tonsil cancer   |                               |                               |                         |
| subjects affected / exposed   | 0 / 130 (0.00%)               | 1 / 132 (0.76%)               | 0 / 129 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 0                         | 0 / 1                         | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0                         | 0 / 0                   |
| Vascular disorders  |                               |                               |                         |
| Hypertension  |                               |                               |                         |
| subjects affected / exposed   | 1 / 130 (0.77%)               | 0 / 132 (0.00%)               | 0 / 129 (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                   |
| Hypertensive crisis   |                               |                               |                         |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Gait disturbance                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| General physical health deterioration                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Reproductive system and breast disorders             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cystocele                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Bronchitis chronic                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Aggression                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Confusional state                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delusion  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Hallucination, visual                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Major depression                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Middle insomnia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Investigations                                  |                 |                 |                 |
| Blood creatine phosphokinase increased          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Electrocardiogram abnormal                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Brain contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 7 / 130 (5.38%) | 1 / 132 (0.76%) | 2 / 129 (1.55%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Rib fracture                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Seroma  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Subcutaneous haematoma                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Traumatic intracranial haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Angina pectoris                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Aortic valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 3 / 129 (2.33%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (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 / 1           |
| Cardiac failure chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve incompetence                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Mitral valve sclerosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Tricuspid valve incompetence                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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                        |                 |                 |                 |
| Amimia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Bradykinesia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Cogwheel rigidity                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Coma  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Dementia with Lewy bodies                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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 / 1           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Subdural hygroma                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed   | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage<br>alternative dictionary used:<br>MedDRA 19 |                 |                 |                 |
| subjects affected / exposed   | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders                                  |                 |                 |                 |
| Haemorrhagic anaemia  |                 |                 |                 |
| subjects affected / exposed   | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Thrombocytopenia  |                 |                 |                 |
| subjects affected / exposed   | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all                       | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders   |                 |                 |                 |
| Macular degeneration  |                 |                 |                 |
| subjects affected / exposed   | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Gastrointestinal disorders  |                 |                 |                 |
| Abdominal discomfort  |                 |                 |                 |
| subjects affected / exposed   | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed   | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Duodenal ulcer haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Gastritis erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 0 / 129 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Large intestine polyp                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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 |                 |                 |                 |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Infections and infestations                     |                 |                 |                 |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Mastoiditis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Otitis media                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 2 / 129 (1.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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 tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 1 / 129 (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           |
| Urinary tract infection                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 0 / 129 (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           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 0 / 129 (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           |

Frequency threshold for reporting non-serious adverse events: 1.5 %

| <b>Non-serious adverse events</b>                     | S 47445 5 mg - W0-W24 | S 47445 15 mg - W0-W24 | S 47445 50 mg - W0-W24 |
|---|-----------------------|------------------------|------------------------|
| Total subjects affected by non-serious adverse events |                       |                        |                        |
| subjects affected / exposed                           | 59 / 129 (45.74%)     | 49 / 130 (37.69%)      | 66 / 132 (50.00%)      |
| Vascular disorders                                    |                       |                        |                        |
| Hypertension  |                       |                        |                        |
| subjects affected / exposed                           | 2 / 129 (1.55%)       | 2 / 130 (1.54%)        | 1 / 132 (0.76%)        |
| occurrences (all)                                     | 2                     | 2                      | 1                      |
| Orthostatic hypotension                               |                       |                        |                        |
| subjects affected / exposed                           | 1 / 129 (0.78%)       | 3 / 130 (2.31%)        | 0 / 132 (0.00%)        |
| occurrences (all)                                     | 1                     | 3                      | 0                      |
| General disorders and administration site conditions  |                       |                        |                        |
| Asthenia  |                       |                        |                        |
| subjects affected / exposed                           | 0 / 129 (0.00%)       | 0 / 130 (0.00%)        | 0 / 132 (0.00%)        |
| occurrences (all)                                     | 0                     | 0                      | 0                      |
| Fatigue   |                       |                        |                        |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                      | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Psychiatric disorders   |                      |                      |                      |
| Aggression<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)           | 0 / 129 (0.00%)<br>0 | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 |
| Confusional state<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Delusion<br>subjects affected / exposed<br>occurrences (all)          | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 |
| Depression<br>subjects affected / exposed<br>occurrences (all)        | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 |
| Initial insomnia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 129 (1.55%)<br>2 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 129 (0.78%)<br>1 | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 |
| Irritability<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>1 | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)      | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |



|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Nightmare<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 129 (0.00%)<br>0 | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 |
| Investigations   |                      |                      |                      |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 129 (1.55%)<br>2 | 1 / 130 (0.77%)<br>1 | 6 / 132 (4.55%)<br>7 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 1 / 130 (0.77%)<br>1 | 1 / 132 (0.76%)<br>1 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 129 (0.78%)<br>1 | 2 / 130 (1.54%)<br>3 | 1 / 132 (0.76%)<br>2 |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)    | 2 / 129 (1.55%)<br>2 | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 129 (0.00%)<br>0 | 3 / 130 (2.31%)<br>3 | 2 / 132 (1.52%)<br>2 |
| Injury, poisoning and procedural complications   |                      |                      |                      |
| Accidental overdose<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 129 (2.33%)<br>3 | 1 / 130 (0.77%)<br>4 | 3 / 132 (2.27%)<br>3 |
| Concussion   |                      |                      |                      |

|                                     |                 |                 |                 |
|-------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed         | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 1               | 0               | 0               |
| Contusion                           |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences (all)                   | 0               | 2               | 1               |
| Fall                                |                 |                 |                 |
| subjects affected / exposed         | 2 / 129 (1.55%) | 3 / 130 (2.31%) | 3 / 132 (2.27%) |
| occurrences (all)                   | 2               | 3               | 3               |
| Ligament sprain                     |                 |                 |                 |
| subjects affected / exposed         | 2 / 129 (1.55%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 2               | 0               | 0               |
| Limb injury                         |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                   | 0               | 0               | 1               |
| Procedural pain                     |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 2 / 130 (1.54%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 0               | 2               | 0               |
| Traumatic haematoma                 |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                   | 0               | 0               | 1               |
| Cardiac disorders                   |                 |                 |                 |
| Atrioventricular block first degree |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 0               | 1               | 0               |
| Bundle branch block left            |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 0               | 0               | 0               |
| Bundle branch block right           |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 0               | 0               | 0               |
| Sinus bradycardia                   |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 2 / 132 (1.52%) |
| occurrences (all)                   | 0               | 0               | 2               |
| Sinus tachycardia                   |                 |                 |                 |
| subjects affected / exposed         | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                   | 0               | 0               | 0               |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all)       | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Nervous system disorders  |                      |                      |                      |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Dementia Alzheimer's type<br>subjects affected / exposed<br>occurrences (all)       | 2 / 129 (1.55%)<br>2 | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 129 (0.78%)<br>1 | 2 / 130 (1.54%)<br>2 | 2 / 132 (1.52%)<br>2 |
| Dizziness exertional<br>subjects affected / exposed<br>occurrences (all)            | 1 / 129 (0.78%)<br>1 | 2 / 130 (1.54%)<br>2 | 0 / 132 (0.00%)<br>0 |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)              | 2 / 129 (1.55%)<br>2 | 1 / 130 (0.77%)<br>1 | 1 / 132 (0.76%)<br>1 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 129 (2.33%)<br>4 | 4 / 130 (3.08%)<br>4 | 4 / 132 (3.03%)<br>4 |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)                | 0 / 129 (0.00%)<br>0 | 3 / 130 (2.31%)<br>3 | 0 / 132 (0.00%)<br>0 |
| Blood and lymphatic system disorders  |                      |                      |                      |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 129 (0.78%)<br>1 | 1 / 130 (0.77%)<br>1 | 3 / 132 (2.27%)<br>3 |
| Normochromic normocytic anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 |
| Ear and labyrinth disorders   |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Tinnitus                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Vertigo positional          |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 2 / 132 (1.52%) |
| occurrences (all)           | 0               | 0               | 2               |
| Gastrointestinal disorders  |                 |                 |                 |
| Abdominal pain              |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Abdominal pain upper        |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 1 / 130 (0.77%) | 4 / 132 (3.03%) |
| occurrences (all)           | 3               | 1               | 4               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 3               | 0               | 0               |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences (all)           | 1               | 2               | 1               |
| Diverticulum intestinal     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Dry mouth                   |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 2 / 132 (1.52%) |
| occurrences (all)           | 0               | 0               | 2               |
| Gastritis                   |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Nausea                      |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences (all)           | 3               | 2               | 1               |
| Vomiting                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hepatobiliary disorders     |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 2 / 129 (1.55%)<br>2 | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 129 (0.78%)<br>1 | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 2 / 130 (1.54%)<br>2 | 2 / 132 (1.52%)<br>2 |
| Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |
| Bronchitis viral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>3 |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Influenza                               |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 1               | 0               | 1               |
| Nasopharyngitis                         |                 |                 |                 |
| subjects affected / exposed             | 4 / 129 (3.10%) | 3 / 130 (2.31%) | 7 / 132 (5.30%) |
| occurrences (all)                       | 4               | 3               | 9               |
| Periodontitis                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Rhinitis                                |                 |                 |                 |
| subjects affected / exposed             | 3 / 129 (2.33%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 3               | 0               | 1               |
| Urinary tract infection                 |                 |                 |                 |
| subjects affected / exposed             | 3 / 129 (2.33%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 4               | 0               | 1               |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Metabolism and nutrition disorders      |                 |                 |                 |
| Acquired mixed hyperlipidaemia          |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 0               | 1               | 1               |
| Decreased appetite                      |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 1               | 2               | 1               |
| Dyslipidaemia                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences (all)                       | 0               | 1               | 0               |
| Glucose tolerance impaired              |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)                       | 0               | 0               | 1               |
| Hypercholesterolaemia                   |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 1 / 130 (0.77%) | 0 / 132 (0.00%) |
| occurrences (all)                       | 1               | 1               | 0               |
| Hyperglycaemia                          |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 129 (0.78%) | 3 / 130 (2.31%) | 2 / 132 (1.52%) |
| occurrences (all)           | 1               | 3               | 2               |
| Hypertriglyceridaemia       |                 |                 |                 |
| subjects affected / exposed | 3 / 129 (2.33%) | 0 / 130 (0.00%) | 1 / 132 (0.76%) |
| occurrences (all)           | 3               | 0               | 1               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 2 / 130 (1.54%) | 1 / 132 (0.76%) |
| occurrences (all)           | 0               | 2               | 1               |
| Hyponatraemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 130 (0.00%) | 0 / 132 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Malnutrition                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 130 (0.77%) | 1 / 132 (0.76%) |
| occurrences (all)           | 0               | 1               | 1               |
| Type 2 diabetes mellitus    |                 |                 |                 |
| subjects affected / exposed | 4 / 129 (3.10%) | 1 / 130 (0.77%) | 1 / 132 (0.76%) |
| occurrences (all)           | 4               | 1               | 1               |

| <b>Non-serious adverse events</b>                     | Placebo - W0-W24  | S 47445 5 mg - W24-W52 | S 47445 15 mg - W24-W52 |
|---|-------------------|------------------------|-------------------------|
| Total subjects affected by non-serious adverse events |                   |                        |                         |
| subjects affected / exposed                           | 60 / 129 (46.51%) | 50 / 119 (42.02%)      | 42 / 115 (36.52%)       |
| Vascular disorders                                    |                   |                        |                         |
| Hypertension  |                   |                        |                         |
| subjects affected / exposed                           | 3 / 129 (2.33%)   | 2 / 119 (1.68%)        | 2 / 115 (1.74%)         |
| occurrences (all)                                     | 3                 | 2                      | 2                       |
| Orthostatic hypotension                               |                   |                        |                         |
| subjects affected / exposed                           | 0 / 129 (0.00%)   | 0 / 119 (0.00%)        | 1 / 115 (0.87%)         |
| occurrences (all)                                     | 0                 | 0                      | 1                       |
| General disorders and administration site conditions  |                   |                        |                         |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Asthenia                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 3 / 119 (2.52%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 3               | 2               |
| Fatigue                     |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 2               | 0               | 1               |
| Oedema peripheral           |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               | 1               |
| Pyrexia                     |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               | 1               |
| Psychiatric disorders       |                 |                 |                 |
| Aggression                  |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Anxiety                     |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 0               | 1               |
| Confusional state           |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 3               | 0               | 0               |
| Delusion                    |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Depression                  |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 2               | 0               | 1               |
| Initial insomnia            |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Insomnia                    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 1 / 119 (0.84%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Irritability                |                 |                 |                 |



|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 2 / 129 (1.55%)<br>2 | 1 / 119 (0.84%)<br>1 | 1 / 115 (0.87%)<br>1 |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 0 / 115 (0.00%)<br>0 |
| Nightmare<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 129 (0.78%)<br>1 | 2 / 119 (1.68%)<br>2 | 0 / 115 (0.00%)<br>0 |
| Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Investigations   |                      |                      |                      |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 129 (0.00%)<br>0 | 2 / 119 (1.68%)<br>2 | 0 / 115 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 2 / 119 (1.68%)<br>2 | 0 / 115 (0.00%)<br>0 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 4 / 129 (3.10%)<br>4 | 5 / 119 (4.20%)<br>5 | 1 / 115 (0.87%)<br>1 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 129 (1.55%)<br>2 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 129 (0.78%)<br>1 | 2 / 119 (1.68%)<br>2 | 1 / 115 (0.87%)<br>1 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 129 (1.55%)<br>2 | 1 / 119 (0.84%)<br>1 | 1 / 115 (0.87%)<br>1 |
| Injury, poisoning and procedural complications   |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Accidental overdose<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 2 / 115 (1.74%)<br>2 |
| Concussion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 115 (1.74%)<br>2 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 129 (1.55%)<br>2 | 1 / 119 (0.84%)<br>1 | 1 / 115 (0.87%)<br>1 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Cardiac disorders   |                      |                      |                      |
| Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 2 / 119 (1.68%)<br>2 | 0 / 115 (0.00%)<br>0 |
| Bundle branch block left<br>subjects affected / exposed<br>occurrences (all)            | 3 / 129 (2.33%)<br>3 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Bundle branch block right<br>subjects affected / exposed<br>occurrences (all)           | 2 / 129 (1.55%)<br>2 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Sinus bradycardia   |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                              | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 129 (1.55%)<br>2 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Nervous system disorders  |                      |                      |                      |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 129 (0.00%)<br>0 | 2 / 119 (1.68%)<br>2 | 0 / 115 (0.00%)<br>0 |
| Dementia Alzheimer's type<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Dizziness exertional<br>subjects affected / exposed<br>occurrences (all)      | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)        | 2 / 129 (1.55%)<br>2 | 4 / 119 (3.36%)<br>6 | 1 / 115 (0.87%)<br>1 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                  | 5 / 129 (3.88%)<br>5 | 5 / 119 (4.20%)<br>5 | 3 / 115 (2.61%)<br>3 |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)          | 3 / 129 (2.33%)<br>3 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Blood and lymphatic system disorders  |                      |                      |                      |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 115 (1.74%)<br>2 |
| Leukopenia  |                      |                      |                      |

|                                 |                 |                 |                 |
|---------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)               | 0               | 0               | 1               |
| Normochromic normocytic anaemia |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)               | 0               | 0               | 1               |
| Ear and labyrinth disorders     |                 |                 |                 |
| Tinnitus                        |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Vertigo positional              |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Gastrointestinal disorders      |                 |                 |                 |
| Abdominal pain                  |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Abdominal pain upper            |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Constipation                    |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Diarrhoea                       |                 |                 |                 |
| subjects affected / exposed     | 4 / 129 (3.10%) | 5 / 119 (4.20%) | 6 / 115 (5.22%) |
| occurrences (all)               | 4               | 5               | 6               |
| Diverticulum intestinal         |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 0               | 0               |
| Dry mouth                       |                 |                 |                 |
| subjects affected / exposed     | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Gastritis                       |                 |                 |                 |
| subjects affected / exposed     | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)               | 1               | 0               | 0               |
| Nausea                          |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 129 (0.78%)<br>1 | 5 / 119 (4.20%)<br>9 | 6 / 115 (5.22%)<br>6 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 2 / 119 (1.68%)<br>2 | 2 / 115 (1.74%)<br>2 |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 1 / 129 (0.78%)<br>1 | 1 / 119 (0.84%)<br>1 | 1 / 115 (0.87%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 4 / 115 (3.48%)<br>4 |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 129 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 0 / 115 (0.00%)<br>0 |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 129 (0.78%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all)  | 2 / 129 (1.55%)<br>2 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |
| Bronchitis viral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 129 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 115 (0.00%)<br>0 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cystitis                                |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Gastroenteritis                         |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 1               | 0               | 0               |
| Influenza                               |                 |                 |                 |
| subjects affected / exposed             | 2 / 129 (1.55%) | 1 / 119 (0.84%) | 1 / 115 (0.87%) |
| occurrences (all)                       | 2               | 1               | 1               |
| Nasopharyngitis                         |                 |                 |                 |
| subjects affected / exposed             | 6 / 129 (4.65%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 7               | 0               | 0               |
| Periodontitis                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 2 / 115 (1.74%) |
| occurrences (all)                       | 0               | 1               | 2               |
| Rhinitis                                |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 1               | 0               | 0               |
| Urinary tract infection                 |                 |                 |                 |
| subjects affected / exposed             | 6 / 129 (4.65%) | 2 / 119 (1.68%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 8               | 3               | 0               |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 6 / 119 (5.04%) | 2 / 115 (1.74%) |
| occurrences (all)                       | 0               | 6               | 2               |
| Metabolism and nutrition disorders      |                 |                 |                 |
| Acquired mixed hyperlipidaemia          |                 |                 |                 |
| subjects affected / exposed             | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)                       | 1               | 0               | 0               |
| Decreased appetite                      |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 4 / 115 (3.48%) |
| occurrences (all)                       | 0               | 1               | 4               |
| Dyslipidaemia                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)                       | 0               | 0               | 1               |
| Glucose tolerance impaired              |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hypercholesterolaemia       |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 2 / 119 (1.68%) | 3 / 115 (2.61%) |
| occurrences (all)           | 1               | 2               | 3               |
| Hyperglycaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               | 1               |
| Hypertriglyceridaemia       |                 |                 |                 |
| subjects affected / exposed | 2 / 129 (1.55%) | 2 / 119 (1.68%) | 0 / 115 (0.00%) |
| occurrences (all)           | 2               | 3               | 0               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 0               | 2               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 1 / 119 (0.84%) | 0 / 115 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hyponatraemia               |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 0               | 2               |
| Malnutrition                |                 |                 |                 |
| subjects affected / exposed | 0 / 129 (0.00%) | 0 / 119 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 0               | 1               |
| Type 2 diabetes mellitus    |                 |                 |                 |
| subjects affected / exposed | 1 / 129 (0.78%) | 0 / 119 (0.00%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |

| <b>Non-serious adverse events</b>                     | S 47445 50 mg - W24-W52 | Placebo - W24-W52 | S 47445 5 mg - W0-W52 |
|---|-------------------------|-------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                         |                   |                       |
| subjects affected / exposed                           | 41 / 115 (35.65%)       | 41 / 119 (34.45%) | 78 / 129 (60.47%)     |
| Vascular disorders                                    |                         |                   |                       |
| Hypertension  |                         |                   |                       |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                            | 2 / 115 (1.74%)<br>2 | 3 / 119 (2.52%)<br>3 | 5 / 129 (3.88%)<br>5 |
| Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all) | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 1 / 129 (0.78%)<br>1 |
| General disorders and administration<br>site conditions                     |                      |                      |                      |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 3 / 129 (2.33%)<br>3 |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)       | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Psychiatric disorders   |                      |                      |                      |
| Aggression<br>subjects affected / exposed<br>occurrences (all)              | 2 / 115 (1.74%)<br>2 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)       | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 129 (0.78%)<br>1 |
| Delusion<br>subjects affected / exposed<br>occurrences (all)                | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>2 | 0 / 129 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)              | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Initial insomnia  |                      |                      |                      |



|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed            | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 0               | 1               | 2               |
| Insomnia                               |                 |                 |                 |
| subjects affected / exposed            | 2 / 115 (1.74%) | 1 / 119 (0.84%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 2               | 1               | 2               |
| Irritability                           |                 |                 |                 |
| subjects affected / exposed            | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 1               | 0               | 2               |
| Mood altered                           |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 0               | 0               | 2               |
| Nightmare                              |                 |                 |                 |
| subjects affected / exposed            | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 1               | 1               | 2               |
| Suicidal ideation                      |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Investigations                         |                 |                 |                 |
| Alanine aminotransferase increased     |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 0               | 0               | 2               |
| Aspartate aminotransferase increased   |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 2 / 129 (1.55%) |
| occurrences (all)                      | 0               | 1               | 2               |
| Blood creatine phosphokinase increased |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 2 / 119 (1.68%) | 7 / 129 (5.43%) |
| occurrences (all)                      | 0               | 2               | 7               |
| Blood lactate dehydrogenase increased  |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Blood pressure increased               |                 |                 |                 |
| subjects affected / exposed            | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)                      | 0               | 0               | 1               |
| Gamma-glutamyltransferase increased    |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 4 / 129 (3.10%)<br>4 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>1 | 1 / 129 (0.78%)<br>1 |
| Injury, poisoning and procedural complications  |                      |                      |                      |
| Accidental overdose<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 115 (1.74%)<br>3 | 2 / 119 (1.68%)<br>2 | 3 / 129 (2.33%)<br>3 |
| Concussion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 129 (0.78%)<br>1 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 115 (1.74%)<br>2 | 2 / 119 (1.68%)<br>2 | 3 / 129 (2.33%)<br>3 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0 |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0 |
| Cardiac disorders   |                      |                      |                      |
| Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Bundle branch block left  |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Bundle branch block right   |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Sinus bradycardia           |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Sinus tachycardia           |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Ventricular extrasystoles   |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 1 / 129 (0.78%) |
| occurrences (all)           | 0               | 1               | 1               |
| Nervous system disorders    |                 |                 |                 |
| Amnesia                     |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)           | 0               | 0               | 2               |
| Dementia Alzheimer's type   |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)           | 0               | 0               | 2               |
| Dizziness                   |                 |                 |                 |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 119 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)           | 2               | 0               | 1               |
| Dizziness exertional        |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)           | 0               | 0               | 1               |
| Dizziness postural          |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 5 / 129 (3.88%) |
| occurrences (all)           | 1               | 1               | 8               |
| Headache                    |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 3 / 119 (2.52%) | 7 / 129 (5.43%) |
| occurrences (all)           | 1               | 4               | 9               |
| Tension headache            |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| Blood and lymphatic system disorders |                 |                 |                 |
| Iron deficiency anaemia              |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Leukopenia                           |                 |                 |                 |
| subjects affected / exposed          | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 1               | 0               | 1               |
| Normochromic normocytic anaemia      |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Tinnitus                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                    | 0               | 0               | 2               |
| Vertigo positional                   |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Gastrointestinal disorders           |                 |                 |                 |
| Abdominal pain                       |                 |                 |                 |
| subjects affected / exposed          | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 3 / 129 (2.33%) |
| occurrences (all)                    | 1               | 1               | 3               |
| Abdominal pain upper                 |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                    | 0               | 0               | 3               |
| Constipation                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 3 / 129 (2.33%) |
| occurrences (all)                    | 0               | 0               | 3               |
| Diarrhoea                            |                 |                 |                 |
| subjects affected / exposed          | 1 / 115 (0.87%) | 2 / 119 (1.68%) | 6 / 129 (4.65%) |
| occurrences (all)                    | 1               | 2               | 6               |
| Diverticulum intestinal              |                 |                 |                 |
| subjects affected / exposed          | 0 / 115 (0.00%) | 2 / 119 (1.68%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 0               | 2               | 0               |
| Dry mouth                            |                 |                 |                 |
| subjects affected / exposed          | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 1               | 1               | 1               |
| Gastritis                            |                 |                 |                 |

|   |                      |                      |                       |
|---|----------------------|----------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>1 | 1 / 129 (0.78%)<br>1  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 3 / 115 (2.61%)<br>3 | 5 / 119 (4.20%)<br>5 | 8 / 129 (6.20%)<br>12 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 3 / 115 (2.61%)<br>3 | 2 / 119 (1.68%)<br>2 | 3 / 129 (2.33%)<br>3  |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0  |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 115 (0.87%)<br>1 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0  |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>3  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 1 / 129 (0.78%)<br>1  |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>2 | 1 / 129 (0.78%)<br>1  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 115 (0.87%)<br>1 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0  |
| Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all)  | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0  |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Bronchitis viral<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 115 (0.00%)<br>0 | 4 / 119 (3.36%)<br>4 | 2 / 129 (1.55%)<br>2 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 1 / 129 (0.78%)<br>1 |
| Periodontitis<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 115 (0.87%)<br>1 | 2 / 119 (1.68%)<br>2 | 1 / 129 (0.78%)<br>1 |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 115 (0.00%)<br>0 | 0 / 119 (0.00%)<br>0 | 3 / 129 (2.33%)<br>3 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>2 | 4 / 129 (3.10%)<br>7 |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 115 (2.61%)<br>3 | 0 / 119 (0.00%)<br>0 | 8 / 129 (6.20%)<br>9 |
| Metabolism and nutrition disorders  |                      |                      |                      |
| Acquired mixed hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 115 (0.00%)<br>0 | 1 / 119 (0.84%)<br>1 | 0 / 129 (0.00%)<br>0 |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 115 (1.74%)<br>2 | 1 / 119 (0.84%)<br>1 | 2 / 129 (1.55%)<br>2 |
| Dyslipidaemia   |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Glucose tolerance impaired  |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hypercholesterolaemia       |                 |                 |                 |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 119 (0.00%) | 4 / 129 (3.10%) |
| occurrences (all)           | 2               | 0               | 4               |
| Hyperglycaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)           | 0               | 0               | 2               |
| Hypertriglyceridaemia       |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 6 / 129 (4.65%) |
| occurrences (all)           | 1               | 1               | 7               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)           | 0               | 0               | 3               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hyponatraemia               |                 |                 |                 |
| subjects affected / exposed | 3 / 115 (2.61%) | 1 / 119 (0.84%) | 0 / 129 (0.00%) |
| occurrences (all)           | 3               | 1               | 0               |
| Malnutrition                |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 119 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Type 2 diabetes mellitus    |                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 119 (0.84%) | 4 / 129 (3.10%) |
| occurrences (all)           | 1               | 1               | 4               |

| <b>Non-serious adverse events</b>                     | S 47445 15 mg - W0-W52 | S 47445 50 mg - W0-W52 | Placebo - W0-W52  |
|---|------------------------|------------------------|-------------------|
| Total subjects affected by non-serious adverse events |                        |                        |                   |
| subjects affected / exposed                           | 70 / 130 (53.85%)      | 79 / 132 (59.85%)      | 76 / 129 (58.91%) |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Vascular disorders                                   |                 |                 |                 |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 4 / 130 (3.08%) | 3 / 132 (2.27%) | 7 / 129 (5.43%) |
| occurrences (all)                                    | 4               | 3               | 7               |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 4 / 130 (3.08%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences (all)                                    | 4               | 1               | 0               |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 1 / 129 (0.78%) |
| occurrences (all)                                    | 2               | 1               | 1               |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 3 / 129 (2.33%) |
| occurrences (all)                                    | 1               | 1               | 3               |
| Oedema peripheral                                    |                 |                 |                 |
| subjects affected / exposed                          | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                                    | 2               | 0               | 0               |
| Pyrexia  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                                    | 1               | 0               | 0               |
| Psychiatric disorders                                |                 |                 |                 |
| Aggression   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 1 / 129 (0.78%) |
| occurrences (all)                                    | 0               | 2               | 1               |
| Anxiety  |                 |                 |                 |
| subjects affected / exposed                          | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 1 / 129 (0.78%) |
| occurrences (all)                                    | 2               | 1               | 1               |
| Confusional state                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                                    | 0               | 0               | 3               |
| Delusion   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 1 / 129 (0.78%) |
| occurrences (all)                                    | 0               | 2               | 2               |
| Depression   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 130 (0.77%) | 2 / 132 (1.52%) | 2 / 129 (1.55%) |
| occurrences (all)                                    | 1               | 2               | 2               |



|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Initial insomnia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 3 / 129 (2.33%)<br>3 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 130 (1.54%)<br>2 | 3 / 132 (2.27%)<br>3 | 2 / 129 (1.55%)<br>2 |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 | 2 / 129 (1.55%)<br>2 |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Nightmare<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 | 2 / 129 (1.55%)<br>2 |
| Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 130 (1.54%)<br>2 | 1 / 132 (0.76%)<br>1 | 1 / 129 (0.78%)<br>1 |
| Investigations   |                      |                      |                      |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 1 / 129 (0.78%)<br>1 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 130 (1.54%)<br>2 | 6 / 132 (4.55%)<br>7 | 6 / 129 (4.65%)<br>6 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 130 (0.77%)<br>1 | 1 / 132 (0.76%)<br>1 | 2 / 129 (1.55%)<br>2 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 3 / 130 (2.31%)<br>4 | 2 / 132 (1.52%)<br>3 | 1 / 129 (0.78%)<br>1 |
| Gamma-glutamyltransferase  |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| increased<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 130 (2.31%)<br>3 | 1 / 132 (0.76%)<br>1 | 1 / 129 (0.78%)<br>1 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 130 (3.08%)<br>4 | 2 / 132 (1.52%)<br>2 | 3 / 129 (2.33%)<br>3 |
| Injury, poisoning and procedural complications  |                      |                      |                      |
| Accidental overdose<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 130 (1.54%)<br>6 | 5 / 132 (3.79%)<br>6 | 3 / 129 (2.33%)<br>3 |
| Concussion<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 130 (1.54%)<br>2 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 130 (2.31%)<br>3 | 2 / 132 (1.52%)<br>2 | 0 / 129 (0.00%)<br>0 |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 4 / 130 (3.08%)<br>4 | 5 / 132 (3.79%)<br>5 | 4 / 129 (3.10%)<br>4 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 130 (0.00%)<br>0 | 1 / 132 (0.76%)<br>1 | 2 / 129 (1.55%)<br>2 |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 130 (1.54%)<br>2 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 130 (0.77%)<br>1 | 2 / 132 (1.52%)<br>2 | 2 / 129 (1.55%)<br>2 |
| Cardiac disorders   |                      |                      |                      |
| Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Bundle branch block left  |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                              | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 3 / 129 (2.33%)<br>3 |
| Bundle branch block right<br>subjects affected / exposed<br>occurrences (all) | 1 / 130 (0.77%)<br>1 | 0 / 132 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Sinus bradycardia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 130 (0.00%)<br>0 | 3 / 132 (2.27%)<br>3 | 2 / 129 (1.55%)<br>2 |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Ventricular extrasystoles<br>subjects affected / exposed<br>occurrences (all) | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |
| Nervous system disorders  |                      |                      |                      |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Dementia Alzheimer's type<br>subjects affected / exposed<br>occurrences (all) | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 | 0 / 129 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 130 (2.31%)<br>3 | 2 / 132 (1.52%)<br>4 | 0 / 129 (0.00%)<br>0 |
| Dizziness exertional<br>subjects affected / exposed<br>occurrences (all)      | 3 / 130 (2.31%)<br>3 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)        | 2 / 130 (1.54%)<br>2 | 2 / 132 (1.52%)<br>2 | 3 / 129 (2.33%)<br>3 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 130 (6.15%)<br>8 | 5 / 132 (3.79%)<br>5 | 7 / 129 (5.43%)<br>9 |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)          | 3 / 130 (2.31%)<br>3 | 0 / 132 (0.00%)<br>0 | 4 / 129 (3.10%)<br>4 |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| Blood and lymphatic system disorders |                 |                 |                 |
| Iron deficiency anaemia              |                 |                 |                 |
| subjects affected / exposed          | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 2               | 1               | 0               |
| Leukopenia                           |                 |                 |                 |
| subjects affected / exposed          | 2 / 130 (1.54%) | 3 / 132 (2.27%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 2               | 4               | 0               |
| Normochromic normocytic anaemia      |                 |                 |                 |
| subjects affected / exposed          | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 2               | 0               | 0               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Tinnitus                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Vertigo positional                   |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 0               | 2               | 1               |
| Gastrointestinal disorders           |                 |                 |                 |
| Abdominal pain                       |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 0               | 1               | 1               |
| Abdominal pain upper                 |                 |                 |                 |
| subjects affected / exposed          | 1 / 130 (0.77%) | 3 / 132 (2.27%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 1               | 3               | 0               |
| Constipation                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Diarrhoea                            |                 |                 |                 |
| subjects affected / exposed          | 8 / 130 (6.15%) | 2 / 132 (1.52%) | 6 / 129 (4.65%) |
| occurrences (all)                    | 8               | 2               | 6               |
| Diverticulum intestinal              |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                    | 0               | 0               | 2               |
| Dry mouth                            |                 |                 |                 |
| subjects affected / exposed          | 0 / 130 (0.00%) | 3 / 132 (2.27%) | 1 / 129 (0.78%) |
| occurrences (all)                    | 0               | 3               | 1               |
| Gastritis                            |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 130 (0.77%)<br>1 | 2 / 132 (1.52%)<br>2 | 2 / 129 (1.55%)<br>2 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 7 / 130 (5.38%)<br>8 | 4 / 132 (3.03%)<br>4 | 6 / 129 (4.65%)<br>6 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 2 / 130 (1.54%)<br>2 | 3 / 132 (2.27%)<br>3 | 2 / 129 (1.55%)<br>2 |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 130 (1.54%)<br>2 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 | 1 / 129 (0.78%)<br>1 |
| Renal and urinary disorders<br>Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)           | 1 / 130 (0.77%)<br>1 | 1 / 132 (0.76%)<br>1 | 1 / 129 (0.78%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 4 / 130 (3.08%)<br>4 | 1 / 132 (0.76%)<br>1 | 1 / 129 (0.78%)<br>1 |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 0 / 129 (0.00%)<br>0 |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 130 (0.00%)<br>0 | 2 / 132 (1.52%)<br>2 | 1 / 129 (0.78%)<br>2 |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 130 (1.54%)<br>2 | 3 / 132 (2.27%)<br>3 | 2 / 129 (1.55%)<br>2 |
| Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all)  | 0 / 130 (0.00%)<br>0 | 0 / 132 (0.00%)<br>0 | 2 / 129 (1.55%)<br>2 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Bronchitis viral                        |                 |                 |                 |
| subjects affected / exposed             | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 0 / 129 (0.00%) |
| occurrences (all)                       | 0               | 3               | 0               |
| Cystitis                                |                 |                 |                 |
| subjects affected / exposed             | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences (all)                       | 2               | 1               | 0               |
| Gastroenteritis                         |                 |                 |                 |
| subjects affected / exposed             | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all)                       | 0               | 0               | 2               |
| Influenza                               |                 |                 |                 |
| subjects affected / exposed             | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 6 / 129 (4.65%) |
| occurrences (all)                       | 1               | 1               | 6               |
| Nasopharyngitis                         |                 |                 |                 |
| subjects affected / exposed             | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Periodontitis                           |                 |                 |                 |
| subjects affected / exposed             | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 2 / 129 (1.55%) |
| occurrences (all)                       | 2               | 1               | 2               |
| Rhinitis                                |                 |                 |                 |
| subjects affected / exposed             | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 1 / 129 (0.78%) |
| occurrences (all)                       | 0               | 1               | 1               |
| Urinary tract infection                 |                 |                 |                 |
| subjects affected / exposed             | 0 / 130 (0.00%) | 1 / 132 (0.76%) | 7 / 129 (5.43%) |
| occurrences (all)                       | 0               | 1               | 10              |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 5 / 130 (3.85%) | 9 / 132 (6.82%) | 6 / 129 (4.65%) |
| occurrences (all)                       | 5               | 13              | 7               |
| Metabolism and nutrition disorders      |                 |                 |                 |
| Acquired mixed hyperlipidaemia          |                 |                 |                 |
| subjects affected / exposed             | 1 / 130 (0.77%) | 1 / 132 (0.76%) | 2 / 129 (1.55%) |
| occurrences (all)                       | 1               | 1               | 2               |
| Decreased appetite                      |                 |                 |                 |
| subjects affected / exposed             | 6 / 130 (4.62%) | 3 / 132 (2.27%) | 1 / 129 (0.78%) |
| occurrences (all)                       | 6               | 3               | 1               |
| Dyslipidaemia                           |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Glucose tolerance impaired  |                 |                 |                 |
| subjects affected / exposed | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Hypercholesterolaemia       |                 |                 |                 |
| subjects affected / exposed | 4 / 130 (3.08%) | 2 / 132 (1.52%) | 1 / 129 (0.78%) |
| occurrences (all)           | 4               | 2               | 1               |
| Hyperglycaemia              |                 |                 |                 |
| subjects affected / exposed | 4 / 130 (3.08%) | 2 / 132 (1.52%) | 0 / 129 (0.00%) |
| occurrences (all)           | 4               | 2               | 0               |
| Hypertriglyceridaemia       |                 |                 |                 |
| subjects affected / exposed | 0 / 130 (0.00%) | 2 / 132 (1.52%) | 3 / 129 (2.33%) |
| occurrences (all)           | 0               | 2               | 3               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 2 / 130 (1.54%) | 0 / 132 (0.00%) | 1 / 129 (0.78%) |
| occurrences (all)           | 2               | 0               | 1               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 130 (0.00%) | 0 / 132 (0.00%) | 0 / 129 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 2 / 130 (1.54%) | 1 / 132 (0.76%) | 0 / 129 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |
| Hyponatraemia               |                 |                 |                 |
| subjects affected / exposed | 2 / 130 (1.54%) | 3 / 132 (2.27%) | 1 / 129 (0.78%) |
| occurrences (all)           | 2               | 3               | 2               |
| Malnutrition                |                 |                 |                 |
| subjects affected / exposed | 2 / 130 (1.54%) | 2 / 132 (1.52%) | 0 / 129 (0.00%) |
| occurrences (all)           | 2               | 2               | 0               |
| Type 2 diabetes mellitus    |                 |                 |                 |
| subjects affected / exposed | 1 / 130 (0.77%) | 2 / 132 (1.52%) | 2 / 129 (1.55%) |
| occurrences (all)           | 1               | 2               | 2               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 05 February 2015 | Update of the inclusion criterion related to estimated Glomerular Filtration Rate (GFR) calculation.  |
| 09 December 2015 | During the optional extension period, the decrease of donepezil dose from 10 mg to 5 mg was permitted if necessary between weeks 28 and 38. Once dose of donepezil decreased to 5 mg, the investigator did not have the possibility to return to 10 mg. |
| 29 February 2016 | Recruitment in Japan was closed further to recruitment difficulties. New countries were added to the list of participating countries in order to reach the planned target of total patients.  |
| 10 November 2016 | Update of the list of concomitant treatments with addition of BCRP substrates.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 26 June 2017 | The main analysis was done in June 2017 with full efficacy and safety data of the mandatory 24-week treatment period. Based on these results, the Sponsor decided to discontinue the study and the development of S47445 in Alzheimer's Disease. | -            |

Notes:

### Limitations and caveats

None reported